Bayer response to NICE clarification letter – aflibercept for visual impairment due to diabetic macular oedema (DMO) (ID717)

Section A: Literature searching

A1. **Priority question: Page 36. Figure 1** (of the company submission). The PRISMA diagram shows that 203 records (80 studies) have been identified in the literature and included in the submission for the assessment of the clinical effectiveness and safety of aflibercept. However, the majority of these records are not accounted for:

- 5 publications for the assessment of aflibercept compared with laser photocoagulation are listed on page 38 but 3 are abstracts and not used as data sources.
- Supplementary data provided from 2 study protocols, 4 clinical study reports, 2 abstract presentations and one assessment report are referred to in page 42.
- 9 studies are considered for the indirect and mixed treatment comparison (page 118).

Please provide a list of the remaining records, detailing their contribution to the assessment or the reasons for their exclusion. For example why was the following study not considered: Roger 2013 (RESPOND – ranibizumab vs laser photocoagulation vs combination)?

Extracts from the complete report for the systematic review and mixed treatment comparison (data on file) have been attached as an Appendix A with this clarification. This extract includes lists of all included (Table 1) and excluded studies (Table 2), and the reasons for exclusion.

The initial literature search did not differentiate between treatments. However, the mixed treatment comparison included studies for aflibercept, laser, ranibizumab (*pro re nata*), dexamethasone intravitreal implant, and fluocinolone acetonide intravitreal implant. Only studies linked to and informing the network were included in the mixed treatment comparison.

Company clinical trial reports and protocols became available internally during the process and, as they were unpublished, were not found in the literature search. They have been used in the submission, in accordance with the NICE process, to provide all the relevant data. The final VISTA/VIVID publication by Korobelnik et al. 2014, the conference presentation, and clinical study reports were more comprehensive than the abstracts and have therefore been used as the primary sources of information.

The RESPOND study (Safety, Efficacy and Cost-efficacy of Ranibizumab (Monotherapy or Combination With Laser) in the Treatment of Diabetic Macular Edema (DME) (NCT01135914) was excluded as there was insufficient information in the abstract presented by Berger A, et al. In: Canadian Journal of Diabetes. Conference: 16th Annual Canadian Diabetes Association/Canadian Society of

Endocrinology and Metabolism Professional Conference and Annual Meetings Montreal, QC Canada. Conference Start: 20131017 Conference End: 20131019. Conference Publication: (var.pagings). 37 (pp S48), 2013. Date of Publication: October 2013. The study was also found listed on clinicaltrials.gov but there was no data available at the time of searching, the last update having been at April 2013. The website, according to the history of changes, was updated with results on 22nd October 2014, after our initial submission. It is unclear what regimen has been used in this study given the limited information available. Three initial monthly doses were given. However, according to the description posted to clinicaltrials.gov, ranibizumab could be 'reapplied', depending on symptoms. There is no data on exposure.

A2. **Page 270. Section 7.4.5** (of the company submission). There appears to be a spelling mistake in the text for bevacizumab. Please clarify that it was spelt correctly in the searches.

Appendix 10.12 of the original submission includes the search strategies for the utility review in which bevacizumab is spelt correctly.

A3. **Page 272 and 343** (of the company submission). The inclusion and exclusion criteria for the search states that '18 year olds' are both included and excluded. Please clarify if they were included in the search.

The review did not select studies by age. However, the Summaries of Product Characteristics (SmPC) for aflibercept, ranibizumab, and dexamethasone intravitreal implant specify the treatment of adults with visual impairment due to DMO. The included studies are in the relevant adult population.

Section B: Clarification on effectiveness data

B1. Please clarify why, apart from fluocinolone and dexamethasone, other corticosteroids were not considered as suitable comparators.

The final scope specified 'corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone)'. These are the only two licensed intravitreal corticosteroids in the UK for DMO. A discussion of the suitability of these comparators is included in Section A of the submission document.

Other corticosteroids have not been included in the final scopes for other previous DMO appraisals at NICE (TA301 fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271) and TA274 ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237)). Similarly, only fluocinolone is included in the scope of the ongoing NICE appraisal of dexamethasone intravitreal implant for diabetic macular oedema (ID653).

B2. **Page 52** (of the company submission)**.** The laser photocoagulation group in the VIVID trial has a higher baseline mean central retinal thickness (CRT) value than the 2 aflibercept groups (540 µm versus 501.9 µm and 518.4 µm respectively). Please clarify if these differences are statistically significant.

A complete analysis is included in the table below. The p value is [redacted].

Table B2: Comparison of central retinal thickness [mm] at baseline (full analysis set)

	Planned Treatment (N)	n	Mean	SD	Min	Q1	Median	Q3	Max
Central retinal thickness [mm] ([redacted])	Laser (N=132)	132	540.3	152.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q4 (N=136)	136	501.9	143.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8 (N=135)	135	518.4	147.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: p-value for comparison of treatment groups calculated with a 2-way ANOVA including geographic region as fixed factor

B3. **Page 52. Table 6** (of the company submission)**.** Please explain why the number of patients who received prior laser photocoagulation in the VIVD trial is not presented.

Data were reported slightly differently for VISTA and VIVID. Unlike the VISTA study, the VIVID study did not report prior laser therapy as a baseline characteristic. However, an ad hoc subgroup analysis of participants with and without prior laser was conducted for this NICE appraisal and integrated data was reported in Table 22-26 of the original submission. VIVID specific data has been provided as part of our response to clarification question B6 in this document.

B4. **Page 53 and 90. Tables 7 and 22** (of the company submission). Please provide the median thickness of the retinas for patients with central retinal thickness (CTR) < 400µm and that of patients with CTR ≥ 400µm for the 3 intervention groups in order to ensure a correct interpretation of the subgroup analysis. *(Laser photocoagulation is considered less effective in thicker retinas, where anti-vascular endothelial growth factors (VEGF) work best).*

An analysis of baseline CRT is included below. In all analyses, the median baseline CRT is [redacted] in the laser arm compared with the 2Q8 arm (the licensed posology in the UK).

Table B4A: Baseline retinal thickness by Baseline CRT group, study eye (Full Analysis Set)

Baseline CRT group, study eye: < 400 µm

Study Identifier			Laser (N=78)	VTE 2Q4 (N=90)	VTE 2Q8 (N=78)	VTE 2 mg Combined (N=168)	Total (N=246)
VISTA	BL Central Retinal Thickness of study eye (microns)	n	[redacted]				
		Mean					
		SD					
		Min					
		Q1					
		Median					
		Q3					
		Max					

Table B4A: Baseline retinal thickness by Baseline CRT group, study eye (Full Analysis Set)

Baseline CRT group, study eye: < 400 µm

Study Identifier			Laser (N=78)	VTE 2Q4 (N=90)	VTE 2Q8 (N=78)	VTE 2 mg Combined (N=168)	Total (N=246)
VIVID	BL Central Retinal Thickness of study eye (microns)	n	[redacted]				
		Mean					
		SD					
		Min					
		Q1					
		Median					
		Q3					
		Max					

Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks; VTE 2Q8 - VTE administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE; Laser - laser therapy at baseline and when re-treatment criteria are met.

Table B4B: Baseline retinal thickness by Baseline CRT group, study eye (Full Analysis Set) (cont.)

Baseline CRT group, study eye: >= 400 µm

Study Identifier			Laser (N=208)	VTE 2Q4 (N=200)	VTE 2Q8 (N=208)	VTE 2 mg Combined (N=408)	Total (N=616)
VISTA	BL Central Retinal Thickness of study eye (microns)	n	[redacted]				
		Mean					
		SD					
		Min					
		Q1					
		Median					
		Q3					
		Max					
VIVID	BL Central Retinal Thickness of study eye (microns)	n					
		Mean					
		SD					
		Min					
		Q1					
		Median					
		Q3					
		Max					

Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks; VTE 2Q8 - VTE administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE; Laser - laser therapy at baseline and when re-treatment criteria are met.

B5. **Priority question: Page 91** (of the company submission)**.** Please provide the corollary of figure 13 for the other subgroups in table 22. Please also provide similar figures for tables 23, 24, 25 and 26.

Figure 13 was provided for the subgroup relating to baseline visual acuity (VA) as this was a pre-specified subgroup and the figure was part of the planned trial analysis. The other subgroups data listed in the table were post hoc analyses conducted specifically for this NICE appraisal, in line with the scope. We have now produced, for the purposes of this request, a further five figures to represent the data already provided in tables 23, 24, 25, and 26 in a diagram format.

Table B5a: LS mean differences (95% CI) for change from baseline to week 52 in ETDRS letter score in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B5b: Differences in proportion of subjects who gained 10 or more letters in the ETDRS letter score from baseline at week 52 in study eye (LOCF) by study and pooled (Full Analysis Set)

[FIGURE DELETED]

Table B5c: Differences in proportion of subjects who gained 15 or more letters in the ETDRS letter score from baseline at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B5d: Differences in proportion of subjects with >= 2-step improvement from baseline in the ETDRS DRSS at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B5e: LS mean differences (95% CI) for change from baseline to week 52 in central retinal thickness (µm) in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

B6. **Page 90-97** (of the company submission)**.** Please provide the corollary of tables 22, 23, 24, 25 and 26 for the **VIVID** trial, also including the corollary of figure 13 for all subgroups. Please provide the corollary of tables 22, 23, 24, 25 and 26 for the **VISTA** trial, also including the corollary of figure 13 for all subgroups.

As described in response to B5, Figure 13 was provided for the subgroup relating to baseline visual acuity (VA) as this was a pre-specified subgroup and the figure was part of the planned trial analysis. The other subgroups data listed in the table were post hoc analyses conducted specifically for this NICE appraisal, in line with the scope. We have now produced, for the purposes of this request, a further 10 figures to represent the data provided in tables 23, 24, 25, and 26 of the original submission in a diagram format and separately by individual VISTA and VIVID study. We have also attached the associated subgroup data tables by individual VISTA and VIVID study in Appendix B.

Table B6a VIVID: LS mean differences (95% CI) for change from baseline to week 52 in ETDRS letter score in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6b VISTA: LS mean differences (95% CI) for change from baseline to week 52 in ETDRS letter score in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6c VIVID: Differences in proportion of subjects who gained 10 or more letters in the ETDRS letter score from baseline at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6d VISTA: Differences in proportion of subjects who gained 10 or more letters in the ETDRS letter score from baseline at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6e VIVID: Differences in proportion of subjects who gained 15 or more letters in the ETDRS letter score from baseline at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6f VISTA: Differences in proportion of subjects who gained 15 or more letters in the ETDRS letter score from baseline at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6g VIVID: Differences in proportion of subjects with >= 2-step improvement from baseline in the ETDRS DRSS at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6h VISTA: Differences in proportion of subjects with >= 2-step improvement from baseline in the ETDRS DRSS at week 52 in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6i VIVID: LS mean differences (95% CI) for change from baseline to week 52 in central retinal thickness (µm) in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

Table B6j VISTA: LS mean differences (95% CI) for change from baseline to week 52 in central retinal thickness (µm) in study eye (LOCF) by subgroup (Full Analysis Set)

[FIGURE DELETED]

B7. **Priority question: Page 169** (of the company submission)**.** Please provide the corollary of table 43 for VISTA, VIVID and the 2 trials pooled separately for:

- the subgroup of patients with CRT thickness ≥ 400µm;
- the subgroup of patients with CRT thickness < 400µm.

Table B7a Risk and odds ratios for aflibercept versus laser

Gain of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	88	151	30	154	48.80%	2.99 [2.11, 4.24]	50.10%	5.77 [3.45, 9.65]
VIVID-DME	72	135	34	132	51.20%	2.07 [1.49, 2.88]	49.90%	3.29 [1.97, 5.52]
Total		**286**		**286**	**100%**	**2.48 [1.73, 3.56]**	**100%**	**4.36 [2.52, 7.56]**
[redacted]	[redacted]							
VIVID <400	[redacted]							
ALL <400					100.00%		100.00%	
VISTA>=400	[redacted]							
VIVID>=400	[redacted]							
ALL >=400					100.00%		100.00%	
Loss of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	[redacted]							
VIVID-DME	[redacted]							
Total					100%		100%	
VISTA <400	[redacted]							
VIVID <400	[redacted]							
ALL <400					100.00%		100.00%	
VISTA>=400	[redacted]							
VIVID>=400	[redacted]							
ALL >=400					100.00%		100.00%	
Gain of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**

VISTA-DME	47	151	12	154	49.70%	3.99 [2.21, 7.23]	50.80%	5.35 [2.70, 10.58]
VIVID-DME	45	135	12	132	50.30%	3.67 [2.03, 6.61]	49.20%	5.00 [2.50, 10.00]
Total		**286**		**286**	**100%**	**3.83 [2.52, 5.81]**	**100%**	**5.17 [3.18, 8.41]**
VISTA <400								
VIVID <400								
ALL <400					100.00%		100.00%	
VISTA>=400								
VIVID>=400								
ALL >=400					100.00%		100.00%	
Loss of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	1	151	14	154	66.00%	0.07 [0.01, 0.55]	65.80%	0.07 [0.01, 0.51]
VIVID-DME	0	135	14	132	34.00%	0.03 [0.00, 0.56]	34.20%	0.03 [0.00, 0.51]
Total		**286**		**286**	**100%**	**0.06 [0.01, 0.29]**	**100%**	**0.05 [0.01, 0.27]**
VISTA<400								
VIVID<400								
ALL <400					100.00%		100.00%	
VISTA>=400								
VIVID>=400								
ALL >=400					100.00%		100.00%	

Please note: 0 has been replaced by 0.5 to enable a calculation of OR and RR

B8. Please provide patient dosing information separately for VISTA and for VIVID for baseline to week 52, including any rescue treatments. Please present in the table below.

Table B8: Number of doses from baseline to week 52

Rescue started week 24	VISTA		VIVID	
	AFB 2Q8	Laser Photocoagulation	AFB 2Q8	Laser Photocoagulation
Patient numbers (n)				
Aflibercept doses total (n)				
Sham injections total (n)				
Laser photocoagulation administrations total (n)				
Sham laser administrations total (n)				

B9. Please provide patient dosing information separately for VISTA and for VIVID for end of week 24 to week 100, including any rescue treatments. Please present in the table below.

Exposure data is reported in the CSR for safety purposes for weeks 0-100 (rescue started week 24). Given the lower priority of this question, the 100 week data is presented here.

Table B9: Number of doses from baseline to week 100

	VISTA		VIVID	
	AFB 2Q8	Laser Photocoagulation	AFB 2Q8	Laser Photocoagulation
Patient numbers (n)	[redacted]			
Aflibercept doses total (n)				
Sham injections total (n)				
Laser photocoagulation administrations total (n)				
Sham laser administrations total (n)				

B10. Please provide the following patient numbers (not percentages) split by the health states used in the economic model for:

- VISTA patients with no bilateral DMO at baseline
- VISTA patients with bilateral DMO at baseline
- VIVID patients with no bilateral DMO at baseline
- VIVID patients with bilateral DMO at baseline

If information on bilateral DMO involvement at baseline is not available, please provide the patient numbers separately for VISTA and for VIVID in the table below.

The VISTA and VIVID studies were primarily designed to evaluate the effect of interventions in the study eye. It should be noted that these analyses use a coding for medical history of 'diabetic retinal edema' in the fellow eye at baseline. However, this data was not collected for analysis of this purpose and therefore may not be the appropriate data for analysing bilateral involvement, due to the nature of the coding and due to the absence of further detail of bilateral involvement.

Data on treatment in the fellow eye was collected for the purpose of safety data, for which treatment exposure in either eye may be relevant. This was referred to in the original submission. For example, in the VISTA study, 198 (65%) of aflibercept patients and in the VIVID study 70 (26%) of aflibercept patients received anti-VEGF treatment in their fellow eye (aflibercept SmPC, September 2014). However, this data on treatment in the fellow eye relates to total exposure during the first 52 weeks and is therefore not baseline data, as requested in this clarification question. Therefore this data has not been presented here.Please also note that in the tables below level relates to health state, as defined in the original submission.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

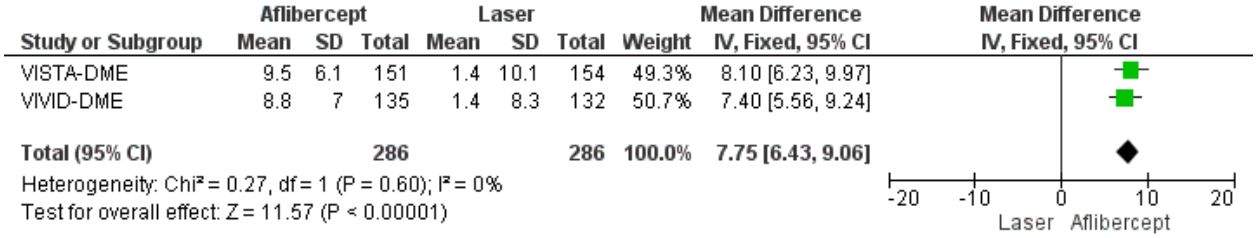
[redacted]

[redacted]

B11. **Page 152. Figure 22** (of the company submission). Please clarify whether the right hand side of the axis favours aflibercept and the left hand side favours laser photocoagulation. The axes appear incorrectly labelled.

The right hand side favours aflibercept.

Figure 22: AFB 2Q8+sham laser vs. laser+sham injection: BCVA mean average change from baseline (LOCF)



B12. **Page 151 onwards** (of the company submission). Please clarify the reason for only including the aflibercept 2Q8 arm in the meta-analysis and network meta-analysis presentation of results.

This is the licensed dosing regimen for aflibercept.in the UK. Similarly, monthly dosing for ranibizumab has been excluded as it is not in line with the SmPC.

B13. **Priority question: Page 169. Table 43** (of the company submission). Please provide the equivalent table for the effect estimates from fixed effect models for both risk ratio (RR) and odds ratio (OR).

The fixed effects efficacy outcomes are included below:

Table B13: Effect estimates by Mantel-Haenszel fixed effects model for dichotomous efficacy outcomes

Gain of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
VISTA-DME	88	151	30	154	46.4%	2.99 [2.11, 4.24]	43.6%	5.77 [3.45, 9.65]
VIVID-DME	72	135	34	132	53.6%	2.07 [1.49, 2.88]	56.4%	3.29 [1.97, 5.52]
Total		**286**		**286**	**100%**	**2.50 [1.97, 3.17]**	**100%**	**4.37 [3.04, 6.29]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
RESTORE	43	115	17	110	50.1%	2.42 [1.47, 3.98]	48.7%	3.27 [1.72, 6.20]
REVEAL	45	133	17	128	49.9%	2.55 [1.54, 4.21]	51.3%	3.34 [1.79, 6.23]
Total		**248**		**238**	**100%**	**2.48 [1.74, 3.54]**	**100%**	**3.30 [2.11, 5.17]**

Loss of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
VISTA-DME	[redacted]							
VIVID-DME								
Total								
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
RESTORE	4	115	14	110	63.7%	0.27 [0.09, 0.80]	63.6%	0.25 [0.08, 0.78]
REVEAL	4	133	8	128	36.3%	0.48 [0.15, 1.56]	36.4%	0.47 [0.14, 1.58]
Total		**248**		**238**	**100%**	**0.35 [0.16, 0.77]**	**100%**	**0.33 [0.14, 0.75]**

Gain of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
VISTA-DME	47	151	12	154	49.5%	3.99 [2.21, 7.23]	50.3%	5.35 [2.70, 10.58]
VIVID-DME	45	135	12	132	50.5%	3.67 [2.03, 6.61]	49.7%	5.00 [2.50, 10.00]
Total		**286**		**286**	**100%**	**3.83 [2.52, 5.82]**	**100%**	**5.17 [3.18, 8.42]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
RESTORE	26	115	9	110	47.4%	2.76 [1.36, 5.63]	46.2%	3.28 [1.46, 7.37]
REVEAL	25	133	10	128	52.6%	2.41 [1.20, 4.81]	53.8%	2.73 [1.25, 5.95]
Total		**248**		**238**	**100%**	**2.58 [1.57, 4.23]**	**100%**	**2.98 [1.70, 5.23]**

Loss of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
VISTA-DME	1	151	14	154	48.6%	0.07 [0.01, 0.55]	48.5%	0.07 [0.01, 0.51]
VIVID-DME	0	135	14	132	51.4%	0.03 [0.00, 0.56]	51.5%	0.03 [0.00, 0.51
Total		**286**		**286**	**100%**	**0.05 [0.01, 0.27]**	**100%**	**0.05 [0.01, 0.25]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
RESTORE	1	115	9	110	64.4%	0.11 [0.01, 0.83]	64.5%	0.10 [0.01, 0.79]

REVEAL	2	133	5	128	35.6%	0.38 [0.08, 1.95]	35.5%	0.38 [0.07, 1.97]
Total		**248**		**238**	**100%**	**0.21 [0.06, 0.71]**	**100%**	**0.20 [0.06, 0.69]**

B14. **Priority question: Page 179. Table 45** (of the company submission)**.** The fixed effect estimate for gain >=10 letters is presented as RR = 0.993 (0.65, 1.52). Please confirm whether this result is the correct way round for estimating the relative effectiveness of aflibercept with ranibizumab?

Yes this is correct.

B15. **Priority question:** Please confirm that the direction of all relative risk (RR) and odds ratio (OR) estimates presented for aflibercept compared with relevant comparators (i.e. ranibizumab, dexamethasone etc) throughout the clinical effectiveness section of the submission are correct.

All of the effect estimates were calculated as aflibercept/laser, ranibizumab/laser, aflibercept/ranibizumab accordingly.

B16. **Page 173** (of the company submission).Please confirm that the results immediately above 'all non-ocular adverse events' relate to all ocular adverse events.

Yes.

B17. **Priority question: Page 171. Table 44** (of the company submission). Please provide the results for the random effects models for the outcome 'all-cause mortality' as they appear to be missing from the submission.

The random effect estimates are included below. Please note that, for the integrated analysis, Korobelnik et al. 2014[1] reported the number of vascular deaths in the 2q8 and laser groups was 2 and 2, respectively and the total number of deaths due to treatment emergent adverse events from baseline to week 52 in these groups was 4 and 2, respectively, with the 2 additional non-vascular deaths in the 2q8 group attributed to B-cell lymphoma and lung neoplasm. The incidences and patterns of deaths were not clinically different among treatment groups.

Table B17: Effect estimates by Mantel-Haenszel fixed and random effects model for dichotomous safety outcomes

Mortality								
Fixed effects								
Study ID	**Aflibercept 2Q8**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
VISTA-DME	0	152	1	154	59.7%	0.34 [0.01, 8.23]	60.5%	0.34 [0.01, 8.30]
VIVID-DME*	5	135	1	133	40.3%	4.93 [0.58, 41.60]	39.5%	5.08 [0.59, 44.05]
Total		**287**		**287**	**100%**	**2.19 [0.49, 9.73]**	**100%**	**2.21 [0.49,**

[1] Korobelnik JF et al. Intravitreal Aflibercept for Diabetic Macular Edema. Ophthalmology 2014; 1-8

								9.93]
Study ID	**Ranibizumab 2**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
RESTORE*	2	112	2	110		0.96 [0.14, 6.67]		0.96 [0.13, 6.91]
Random effects								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
VISTA-DME	0	152	1	154	39.8%	0.34 [0.01, 8.23]	40.1%	0.34 [0.01, 8.30]
VIVID-DME	5	135	1	133	60.2%	4.93 [0.58, 41.60]	59.9%	5.08 [0.59, 44.05]
Total		**287**		**287**	**100%**	**1.70 [0.13, 22.19]**	**100%**	**1.71 [0.13, 23.23]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Fixed, 95% CI**
RESTORE**	2	112	2	110		0.96 [0.39, 2.32]		0.96 [0.13, 6.91]

*Note: One death (MI) occurred in the 2q8 group in VIVID in year 2 (406 and 77 days after the first and last active injections, respectively), but due to data conventions it was included in the Year 1 clinical database

** Only reported in a single study. No meta-analysis possible. Point estimates are reported for completeness

B18. **Page 60. Table 12** (of the company submission). Please provide the reasons for study discontinuation separately for the aflibercept and laser photocoagulation arms of VISTA and VIVID.

This is included in Figure 5 to Figure 7 of the original submission.

B19. **Priority question: Page 209. Table 60** (of the company submission). Please clarify if the difference between laser photocoagulation and each of the aflibercept group, and the difference between laser photocoagulation and the aggregated aflibercept result is statistically significant.

The P-values below show that any differences in deaths during week 0-100 of the VISTA and VIVID studies (safety population)[2] were not significant.

[2] Midena E for the VIVID^{DME} and VISTA^{DME} study investigators. Intravitreal Aflibercept for Diabetic Macular Edema. 100-week results from the VIVID^{DME} and VISTA^{DME} studies. Euretina (London), September 2014.

Table B19a VISTA and VIVID integrated - Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q4 (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=287 (100%)	VTE 2Q4 N=291 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	**4 (1.4%)**	**12 (4.1%)**	**2.96 (0.97;9.07)**	**0.06**
Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.3%)		
Cerebrovascular accident	0	1 (0.3%)		
Cerebral injuries NEC	0	1 (0.3%)		
Brain herniation	0	1 (0.3%)		
Colorectal neoplasms malignant	0	1 (0.3%)		
Colon cancer	0	1 (0.3%)		
Death and sudden death	1 (0.3%)	1 (0.3%)	0.99 (0.06;15.69)	>0.99
Death	0	1 (0.3%)		
Sudden cardiac death	1 (0.3%)	0		
General signs and symptoms NEC	1 (0.3%)	0		
Multi-organ failure	1 (0.3%)	0		
Heart failures NEC	0	1 (0.3%)		
Cardiac failure acute	0	1 (0.3%)		
Ischaemic coronary artery disorders	1 (0.3%)	3 (1.0%)	2.96 (0.31;28.28)	0.35
Acute myocardial infarction	1 (0.3%)	0		
Myocardial infarction	0	3 (1.0%)		
Lower respiratory tract and lung infections	0	1 (0.3%)		
Pneumonia	0	1 (0.3%)		
Renal failure and impairment	0	1 (0.3%)		
Renal failure chronic	0	1 (0.3%)		
Ventricular arrhythmias and cardiac arrest	1 (0.3%)	2 (0.7%)	1.97 (0.18;21.63)	0.58
Cardiac arrest	1 (0.3%)	1 (0.3%)	0.99 (0.06;15.69)	>0.99
Pulseless electrical activity	0	1 (0.3%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19b: VISTA AND VIVID Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q8 (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=287 (100%)	VTE 2Q8 N=287 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	**4 (1.4%)**	**10 (3.5%)**	**2.50 (0.79;7.88)**	**0.12**

Table B19b: VISTA AND VIVID Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q8 (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	**Laser N=287 (100%)**	**VTE 2Q8 N=287 (100%)**	**Risk ratio and 95% confidence interval**	**p-value of CMH Test**
B-cell lymphomas NEC	0	1 (0.3%)		
B-cell lymphoma	0	1 (0.3%)		
Cardiac hypertensive complications	0	1 (0.3%)		
Hypertensive heart disease	0	1 (0.3%)		
Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.3%)		
Cerebrovascular accident	0	1 (0.3%)		
Death and sudden death	1 (0.3%)	0		
Sudden cardiac death	1 (0.3%)	0		
General signs and symptoms NEC	1 (0.3%)	0		
Multi-organ failure	1 (0.3%)	0		
Heart failures NEC	0	1 (0.3%)		
Cardiac failure	0	1 (0.3%)		
Ischaemic coronary artery disorders	1 (0.3%)	1 (0.3%)	1.00 (0.06;15.91)	>0.99
Acute myocardial infarction	1 (0.3%)	0		
Myocardial infarction	0	1 (0.3%)		
Lower respiratory tract and lung infections	0	1 (0.3%)		
Pneumonia	0	1 (0.3%)		
Non-site specific necrosis and vascular insufficiency NEC	0	1 (0.3%)		
Arteriosclerosis	0	1 (0.3%)		
Respiratory tract and pleural neoplasms malignancy unspecified NEC	0	1 (0.3%)		
Lung neoplasm	0	1 (0.3%)		
Ventricular arrhythmias and cardiac arrest	1 (0.3%)	3 (1.0%)	3.00 (0.31;28.67)	0.34
Cardiac arrest	1 (0.3%)	2 (0.7%)	2.00 (0.18;21.93)	0.57
Ventricular arrhythmia	0	1 (0.3%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2Q8 - VEGF Trap-Eye (VTE) administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19c VISTA AND VIVID Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2 mg Combined (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=287 (100%)	VTE 2 mg Combined N=578 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	**4 (1.4%)**	**22 (3.8%)**	**2.73 (0.95;7.85)**	**0.06**

Table B19c VISTA AND VIVID Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2 mg Combined (Safety Analysis Set)				
High level term Preferred term MedDRA version 17.0	Laser N=287 (100%)	VTE 2 mg Combined N=578 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
B-cell lymphomas NEC	0	1 (0.2%)		
B-cell lymphoma	0	1 (0.2%)		
Cardiac hypertensive complications	0	1 (0.2%)		
Hypertensive heart disease	0	1 (0.2%)		
Central nervous system haemorrhages and cerebrovascular accidents	0	2 (0.3%)		
Cerebrovascular accident	0	2 (0.3%)		
Cerebral injuries NEC	0	1 (0.2%)		
Brain herniation	0	1 (0.2%)		
Colorectal neoplasms malignant	0	1 (0.2%)		
Colon cancer	0	1 (0.2%)		
Death and sudden death	1 (0.3%)	1 (0.2%)	0.50 (0.03;7.91)	0.62
Death	0	1 (0.2%)		
Sudden cardiac death	1 (0.3%)	0		
General signs and symptoms NEC	1 (0.3%)	0		
Multi-organ failure	1 (0.3%)	0		
Heart failures NEC	0	2 (0.3%)		
Cardiac failure	0	1 (0.2%)		
Cardiac failure acute	0	1 (0.2%)		
Ischaemic coronary artery disorders	1 (0.3%)	4 (0.7%)	1.99 (0.22;17.69)	0.54
Acute myocardial infarction	1 (0.3%)	0		
Myocardial infarction	0	4 (0.7%)		
Lower respiratory tract and lung infections	0	2 (0.3%)		
Pneumonia	0	2 (0.3%)		
Non-site specific necrosis and vascular insufficiency NEC	0	1 (0.2%)		
Arteriosclerosis	0	1 (0.2%)		
Renal failure and impairment	0	1 (0.2%)		
Renal failure chronic	0	1 (0.2%)		
Respiratory tract and pleural neoplasms malignancy unspecified NEC	0	1 (0.2%)		
Lung neoplasm	0	1 (0.2%)		
Ventricular arrhythmias and cardiac arrest	1 (0.3%)	5 (0.9%)	2.48 (0.29;21.15)	0.41
Cardiac arrest	1 (0.3%)	3 (0.5%)	1.49 (0.16;14.26)	0.73
Pulseless electrical activity	0	1 (0.2%)		

Table B19c VISTA AND VIVID Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2 mg Combined (Safety Analysis Set)				
High level term Preferred term MedDRA version 17.0	Laser N=287 (100%)	VTE 2 mg Combined N=578 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Ventricular arrhythmia	0	1 (0.2%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2 mg Combined = VTE 2Q4 + VTE 2Q8.
Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks.
Note: VTE 2Q8 - VEGF Trap-Eye (VTE) administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19c: VISTA: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q4 (Safety Analysis Set)				
High level term Preferred term MedDRA version 17.0	**Laser N=154 (100%)**	**VTE 2Q4 N=155 (100%)**	**Risk ratio and 95% confidence interval**	**p-value of CMH Test**
Number of subjects with at least one adverse event leading to death	3 (1.9%)	8 (5.2%)	2.65 (0.72;9.80)	0.14
Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.6%)		
Cerebrovascular accident	0	1 (0.6%)		
Death and sudden death	1 (0.6%)	1 (0.6%)	0.99 (0.06;15.74)	>0.99
Death	0	1 (0.6%)		
Sudden cardiac death	1 (0.6%)	0		
General signs and symptoms NEC	1 (0.6%)	0		
Multi-organ failure	1 (0.6%)	0		
Heart failures NEC	0	1 (0.6%)		
Cardiac failure acute	0	1 (0.6%)		
Ischaemic coronary artery disorders	0	1 (0.6%)		
Myocardial infarction	0	1 (0.6%)		
Lower respiratory tract and lung infections	0	1 (0.6%)		
Pneumonia	0	1 (0.6%)		
Renal failure and impairment	0	1 (0.6%)		
Renal failure chronic	0	1 (0.6%)		
Ventricular arrhythmias and cardiac arrest	1 (0.6%)	2 (1.3%)	1.99 (0.18;21.69)	0.57
Cardiac arrest	1 (0.6%)	1 (0.6%)	0.99 (0.06;15.74)	>0.99
Pulseless electrical activity	0	1 (0.6%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19d: VISTA: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q8 (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=154 (100%)	VTE 2Q8 N=152 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	**3 (1.9%)**	**4 (2.6%)**	**1.35 (0.31;5.93)**	**0.69**
Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.7%)		
Cerebrovascular accident	0	1 (0.7%)		
Death and sudden death	1 (0.6%)	0		
Sudden cardiac death	1 (0.6%)	0		
General signs and symptoms NEC	1 (0.6%)	0		
Multi-organ failure	1 (0.6%)	0		
Non-site specific necrosis and vascular insufficiency NEC	0	1 (0.7%)		
Arteriosclerosis	0	1 (0.7%)		
Ventricular arrhythmias and cardiac arrest	1 (0.6%)	2 (1.3%)	2.03 (0.19;22.11)	0.56
Cardiac arrest	1 (0.6%)	2 (1.3%)	2.03 (0.19;22.11)	0.56

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2Q8 - VEGF Trap-Eye (VTE) administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19e: VISTA: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2 mg Combined (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=154 (100%)	VTE 2 mg Combined N=307 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	**3 (1.9%)**	**12 (3.9%)**	**2.01 (0.57;7.01)**	**0.27**
Central nervous system haemorrhages and cerebrovascular accidents	0	2 (0.7%)		
Cerebrovascular accident	0	2 (0.7%)		
Death and sudden death	1 (0.6%)	1 (0.3%)	0.50 (0.03; 7.97)	0.62
Death	0	1 (0.3%)		
Sudden cardiac death	1 (0.6%)	0		
General signs and symptoms NEC	1 (0.6%)	0		
Multi-organ failure	1 (0.6%)	0		
Heart failures NEC	0	1 (0.3%)		
Cardiac failure acute	0	1 (0.3%)		
Ischaemic coronary artery disorders	0	1 (0.3%)		
Myocardial infarction	0	1 (0.3%)		
Lower respiratory tract and lung infections	0	1 (0.3%)		
Pneumonia	0	1 (0.3%)		
Non-site specific necrosis and vascular insufficiency NEC	0	1 (0.3%)		
Arteriosclerosis	0	1 (0.3%)		
Renal failure and impairment	0	1 (0.3%)		
Renal failure chronic	0	1 (0.3%)		
Ventricular arrhythmias and cardiac arrest	1 (0.6%)	4 (1.3%)	2.01 (0.23;17.80)	0.53
Cardiac arrest	1 (0.6%)	3 (1.0%)	1.50 (0.16;14.35)	0.72
Pulseless electrical activity	0	1 (0.3%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2 mg Combined = VTE 2Q4 + VTE 2Q8.
Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks.
Note: VTE 2Q8 - VEGF Trap-
Eye (VTE) administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19f: VIVID: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q4 (Safety Analysis Set)				
High level term Preferred term MedDRA version 17.0	Laser N=133 (100%)	VTE 2Q4 N=136 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	**1 (0.8%)**	**4 (2.9%)**	**3.91 (0.44;34.54)**	**0.22**
Cerebral injuries NEC	0	1 (0.7%)		
Brain herniation	0	1 (0.7%)		
Colorectal neoplasms malignant	0	1 (0.7%)		
Colon cancer	0	1 (0.7%)		
Ischaemic coronary artery disorders	1 (0.8%)	2 (1.5%)	1.96 (0.18;21.31)	0.58
Acute myocardial infarction	1 (0.8%)	0		
Myocardial infarction	0	2 (1.5%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19g: VIVID: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q8 (Safety Analysis Set)				
High level term Preferred term MedDRA version 17.0	Laser N=133 (100%)	VTE 2Q8 N=135 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	1 (0.8%)	6 (4.4%)	5.91 (0.72;48.44)	0.10
B-cell lymphomas NEC	0	1 (0.7%)		
B-cell lymphoma	0	1 (0.7%)		
Cardiac hypertensive complications	0	1 (0.7%)		
Hypertensive heart disease	0	1 (0.7%)		
Heart failures NEC	0	1 (0.7%)		
Cardiac failure	0	1 (0.7%)		
Ischaemic coronary artery disorders	1 (0.8%)	1 (0.7%)	0.99 (0.06;15.59)	>0.99
Acute myocardial infarction	1 (0.8%)	0		
Myocardial infarction	0	1 (0.7%)		
Lower respiratory tract and lung infections	0	1 (0.7%)		
Pneumonia	0	1 (0.7%)		
Respiratory tract and pleural neoplasms malignancy unspecified NEC	0	1 (0.7%)		
Lung neoplasm	0	1 (0.7%)		
Ventricular arrhythmias and cardiac arrest	0	1 (0.7%)		

Table B19g: VIVID: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2Q8 (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=133 (100%)	VTE 2Q8 N=135 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Ventricular arrhythmia	0	1 (0.7%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2Q8 - VEGF Trap-Eye (VTE) administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Table B19h: VIVID: Number of subjects with adverse events leading to death by high level term and preferred term: Laser vs. VTE 2 mg Combined (Safety Analysis Set)

High level term Preferred term MedDRA version 17.0	Laser N=133 (100%)	VTE 2 mg Combined N=271 (100%)	Risk ratio and 95% confidence interval	p-value of CMH Test
Number of subjects with at least one adverse event leading to death	1 (0.8%)	10 (3.7%)	4.91 (0.63;37.94)	0.13
B-cell lymphomas NEC	0	1 (0.4%)		
B-cell lymphoma	0	1 (0.4%)		
Cardiac hypertensive complications	0	1 (0.4%)		
Hypertensive heart disease	0	1 (0.4%)		
Cerebral injuries NEC	0	1 (0.4%)		
Brain herniation	0	1 (0.4%)		
Colorectal neoplasms malignant	0	1 (0.4%)		
Colon cancer	0	1 (0.4%)		
Heart failures NEC	0	1 (0.4%)		
Cardiac failure	0	1 (0.4%)		
Ischaemic coronary artery disorders	1 (0.8%)	3 (1.1%)	1.47 (0.15;14.02)	0.74
Acute myocardial infarction	1 (0.8%)	0		
Myocardial infarction	0	3 (1.1%)		
Lower respiratory tract and lung infections	0	1 (0.4%)		
Pneumonia	0	1 (0.4%)		
Respiratory tract and pleural neoplasms malignancy unspecified NEC	0	1 (0.4%)		
Lung neoplasm	0	1 (0.4%)		
Ventricular arrhythmias and cardiac arrest	0	1 (0.4%)		
Ventricular arrhythmia	0	1 (0.4%)		

Note: Laser - laser therapy at baseline and when re-treatment criteria are met.
Note: VTE 2 mg Combined = VTE 2Q4 + VTE 2Q8.
Note: VTE 2Q4 - VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks.
Note: VTE 2Q8 - VEGF Trap-Eye (VTE) administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Section C: Clarification on cost-effectiveness data

C1. **Priority question: Page 274. Figure 69** (of the company submission). The PRISMA diagram states that 67 studies were included in the health-related quality of life review of which only 7 are cited in the submission. Please provide a list of the remaining studies, detailing their contribution to the assessment of health-related quality of life data.

The studies are listed below and a description of their usefulness given in Table C1:

- Abell, R et al. "Cost-Effectiveness of Femtosecond Laser-Assisted Cataract Surgery versus Phacoemulsification Cataract Surgery." Ophthalmology 121.1 (2014): 10-16.
- Alavi, Y, et al. "Developing an algorithm to convert routine measures of vision into utility values for Glaucoma." Ophthalmic epidemiology 18.5 (2011): 233-243.
- Aspinall, PA., et al. "Evaluation of quality of life and priorities of patients with glaucoma." Investigative ophthalmology & visual science 49.5 (2008): 1907-1915.
- Aspinall, PA., et al. "Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration." British journal of ophthalmology 91.6 (2007): 766-772.
- Bansback, N., et al. "Determinants of health related quality of life and health state utility in patients with age related macular degeneration: the association of contrast sensitivity and visual acuity." Quality of Life Research 16.3 (2007): 533-543.
- Bass, EB. et al "Patients' Perceptions of the Value of Current Vision: Assessment of Preference Values Among Patients With Subfoveal Choroidal Neovascularization--The Submacular Surgery Trials Vision Preference Value Scale: SST Report No. 6." Archives of ophthalmology 122.12 (2004): 1856.
- Black, N., et al. "Is there over utilisation of cataract surgery in England?." British Journal of Ophthalmology 93.1 (2009): 13-17.
- Blackhouse, G, et al. "Research Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Canada." (2010).
- Buchholz, P, et al. "Utility assessment to measure the impact of dry eye disease." The ocular surface 4.3 (2006): 155-161.
- Burr JM et al, "Surveillance for Ocular Hypertension: An Evidence Synthesis and Economic Evaluation.," Health technology assessment (Winchester, England), 16 (2012), 1-271, iii-iv
- Butt, Thomas, et al. "Patient and public preferences for health states associated with AMD." Optometry & Vision Science 90.8 (2013): 855-860.
- Chakravarthy, U, et al. "Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial." Ophthalmology 119.7 (2012): 1399-1411.
- Chia, EM, et al. "Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study." Investigative ophthalmology & visual science 45.1 (2004): 71-76.
- Chia, EM., et al. "Unilateral visual impairment and health related quality of life: the Blue Mountains Eye Study." British journal of ophthalmology 87.4 (2003): 392-395.
- Clark, A, et al. "Quality of life after postoperative endophthalmitis." Clinical & experimental ophthalmology 36.6 (2008): 526-531.

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Table C1: Included quality of life studies from the systematic review, including analysis of usefulness

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
Loftus, JV	DME and Diabetes	EQ-5D for baseline DME versus Diabetic patients.	Utility specific to DME and Diabetes population.	Study described health states which are not usable in current model.	Multicentre trial (including Australia/Brazil/Canada/ UK)
Fenwick, EK	Other retinal disorders (Complication: Diabetic/DR/DME/Vision Impairment Diabetic complications)	EQ-5D utility values per number of complications.	Utility value is within the scope of a DME population.	Study described health states which are not usable in current model.	Australia
Lloyd, A	Other retinal disorders (DR patients Diabetes control group General Public)	Standard Gamble / EQ-5D single index per VA state	Utility value provided for varying VA states	Study described health states which are not usable in current model	UK
Rodgers, M	Other retinal disorders (Diabetes patients & DR complications)	Mean utility for DR and severe VI patients	Utility value reported for varying levels of visual impairment	Study described health states which are not usable in current model	UK
Szabo, SM	Other retinal disorders (DR)	TTO for varying VA states	Utility value provided for varying VA states.	Sample size < 100	Canada
Finger, RP	Other retinal / vision-related disorders (Ocular condition (patients only) : 1085 (80%) AMD 243(23%) DR/DME 730(67%) Other 109 (10%))	EQ-5D NZ VAS for mild / moderate / severe levels of VI	Utility reported for varying levels of VA.	Study described health states which are not usable in current model.	Germany & Australia
Sharma, S	Other retinal / vision-related disorders (Visual loss secondary to diabetic retinopathy (20/30 or worse in at least one eye))	TTO for varying VA states	Utility value provided for varying VA states.	Inconsistent or counterintuitive findings; (where patients in better health states have worse utility values compared to the patients in worse health states)	Canada
Alavi, Y	Wider vision-related disorders (Glaucoma patients)	Utility per logmar VA state	Utility provided per VA state.	Utility not derived from DME population.	UK

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
Aspinall, PA	Wider vision-related disorders (AMD)	Mean TTO per logmar VA state.	Utility provided per VA state.	Utility not derived from DME population.	UK
Aspinall, PA	Wider vision-related disorders (Glaucoma)	EQ-5D per Mild / Moderate / Severe VA state	Utility provided per varying levels of visual impairment.	Study described health states which are not usable in current model.	UK
Bansback, N	Wider vision-related disorders (ARMD)	Mean TTO, HUI, SG.	A range of utility inputs have been used in the cost effectiveness analysis.	Study described health states which are not usable in current model.	UK
Bass, EB Submacular Surgery Trials Research Group	Wider vision-related disorders (Patients with submacular CNV)	Utility value for AMD / Cataract / Complete blindness.	Various literature sources used to elicit utility values.	Utility value for cataract estimated on a rating scale as opposed to EQ-5D specific values.	Multicentre trial
Butt, T	Wider vision-related disorders (AMD)	EQ-5D / SF-6D / TTO for AMD patients	Study Population used to elicit utility values.	Sample size < 100 Utility value not provided per VA state.	UK
Clarke, PM UK Prospective Diabetes Study (UKDPS) Group	Wider vision-related disorders (Newly diagnosed Type 2 diabetes)	EQ-5D of blindness	Utility elicited from study population.	Utility value not provided per state of vision decline.	UK
Clarke, PM	Wider vision-related disorders (Type 2 diabetes)	SF-36 / SF-6D per logmar VA state	Utility elicited from study population per VA state.	Study described health states which are not usable in current model.	UK
Chia, E-M	Wider vision-related disorders (Non-correctable unilateral visual impairment)	SF-36 per VA state / cataract	HRQOL per VA state presented from a large multicentre patient population.	SF-36 values will need to be converted to single utility values. Study described health states which are not usable in current model.	Australia
Crewe, JM	Wider vision-related disorders (Legally blind & severely visually impaired)	TTO per logmar VA state	Utility value presented per VA state.	Inconsistent or counterintuitive findings;	Australia

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
				(where patients in better health states have worse utility values compared to the patients in worse health states)	
Cruess, A	Wider vision-related disorders (nvAMD)	EQ-5D of nvAMD patients per age group	Age specific utility value presented.	Study described health states which are not usable in current model.	Canada
Colquitt, J L	Wider vision-related disorders (Age-related macular degeneration (subfoveal CNV associated with wet AMD.))	TTO / SG per VA health state	A broad and thorough systematic search of the literature identified all English-language RCTs on ranibizumab and pegaptanib. Utility presented per VA state.	Utility not specific to DME population.	UK
Czoski-Murray, C	Wider vision-related disorders (General Population with varying lens)	Utility per VA group	Study provides utility values for 4 VA health states expressed in terms of logmar values based on three different contact lens type and a population representative of a ARMD simulated state.	Utility not specific to DME population.	UK
Espallargues, M	Wider vision-related disorders (ARMD)	EQ-5D per logmar VA state	Utility value presented per VA state.	Inconsistent or counterintuitive findings; (where patients in better health states have worse utility values compared to the patients in worse health states)	UK
Frick, KD	Wider vision-related disorders (Uveitis)	EQ-5D per logmar VA state	Utility value presented per VA state.	Study described health states which are not usable in current model.	UK, US & Australia
Ghazi-Nouri, SMS	Wider vision-related disorders (Patients due to	SF-36 Mean scores	Both HRQOL and VRQOL reported and compared for	Study described health states which are not usable	UK

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
	undergo ERM peel)		the study population.	in current model.	
Hollands, H	Wider vision-related disorders (Visually impaired)	SF-12 summary scores per VA state	HRQOL reported per VA state.	Study described health states which are not usable in current model.	Canada
Chakravarthy, U	Wider vision-related disorders (N-AMD)	EQ-5D mean value	Utility elicited from study population.	Utility not provided per VA state.	UK
Karnon, J	Wider vision-related disorders (AMD)	TTO (age / non-age specific) per VA state.	Utility value provided per VA state.	Utility values not specific to DME population.	UK
Levy, AR	Wider vision-related disorders (Bilateral neovascular age-related macular degeneration)	Mean TTO per VA state	Utility reported per VA state.	Utility not specific to a DME population.	Canada
Lotery, A	Wider vision-related disorders (NV-AMD)	EQ-5D range for normal / mild / severe / blind health states	Utility value presented per VA level.	Inconsistent or counterintuitive findings; (where patients in better health states have worse utility values compared to the patients in worse health states)	UK
Malvankar M	Wider vision-related disorders (Patients diagnosed with Keratoconus)	Median VISQOL for BSE / WSE	Utility presented for varying levels of VA states.	Study described health states which are not usable in current model.	Australia
Mathew, RS	Wider vision-related disorders (AMD)	SF-36 values AMD versus Control	HRQOL summary scores reported per varying levels of VA states.	Study described health states which are not usable in current model.	Australia
Mo, F	Wider vision-related disorders (Cataract patients)	HUI value for age / gender specific cataract patients	Age and Gender specific utility index reported for cataract patients.	EQ-5D usable input not reported.	Canada
Murphy, C	Wider vision-related disorders (Uveitis)	SF-36 per VA state	HRQOL reported per VA state.	Study described health states which are not usable in current model	UK
Murphy, C	Wider vision-related disorders (Uveitis)	SF-36 / TTO per VA state	Utility value per VA state.	Study described health states which are not usable in current model	UK
Reeves, BC	Wider vision-related disorders (NV-AMD)	SF-36 for 5 letter vision loss	HRQOL reporting for varying VA states.	Utility for DME specific population not reported.	UK

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
				SF-36 values will have to be converted to utility scores.	
Reeves, BC	Wider vision-related disorders (NV-AMD)	Utility values per vision state Utility gain from cataract surgery.	Utility presented per VA state.	All secondary sources have been extracted previously.	UK
Smith, DH	Wider vision-related disorders (AMD)	TTO per VA state	Utility provided per VA state.	Utility values not specific to DME patient population.	UK
Soubrane, G	Wider vision-related disorders (NV-AMD)	Utility value of nv-AMD versus control	Utility presented for varying levels of VA states.	Inconsistent or counterintuitive findings; (where patients in better health states have worse utility values compared to the patients in worse health states)	Canada / UK
Tahhan, N	Wider vision-related disorders (Refractory error)	Comorbidity adjusted utility per VA state	Utility presented per VA state.	Study described health states which are not usable in current model	Australia
Gupta, OP	Wider vision-related disorders (Patients affected by Epiretinal Membrane)	TTO values for cataract / Retinal Tear / Endopthalmitis /	Utility values reported for a number of adverse events of interest in the Australian model.	Population specific to epiretinal membrane tear.	Australia / US
Ontario Health Technology	Wider vision-related disorders (Age related cataracts)	Disutility for retinal detachment	Various literature sources were pooled together for the reported utility values.	Only conditional probability of retinal detachment reported. Utility / disutility value cannot be utilised within the current scope of the model.	Canada
Hopley, C	Wider vision-related disorders (AMD)	TTO per VA state / loss of VA lines	Utility presented per VA state.	Utility not specific to DME population	Australia
Pager, CK	Wider vision-related disorders (Cataract)	Utility value for pre / post-operative value	Utility presented for two vision states, one before and one after surgery.	Utility value provided in a format not currently usable within the scope of the model.	Australia
Pham, T Q	Wider vision-related	SF-12 Summary score for	Utility was also provided for	Study described health	Australia

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
	disorders (Patients who had undergone cataract surgery)	cataract patients	follow up VA changes.	states which are not usable in current model	
Sahebjada, S	Wider vision-related disorders (Cataract surgery patients)	Utility associated with Endophthalimitis / MACULAR Edema after Cataract surgery	Various literature sources have been used to narrow down the utility values for the adverse events.	Study described health states which are not usable in current model. (Overall utility measure not provided for Endophthalmitis)	Canada
Sharma S	Wider vision-related disorders (AMD)	Utility loss due to adverse event.	Utility expressed at the loss per lines of vision.	Not a DME specific population.	Canada
Sharma S	Wider vision-related disorders (Macular Degeneration)	Utility value for adverse events	The study population has not been used to elicit the utility values, therefore this article is a good source for adverse event utility values for Canada. Literature value for Retinal Detachment (Busbee 2002) good source for adverse events. Busbee 2002 is commonly used across articles for utility values specific to adverse events related to vision related disorders. Therefore this is a reliable secondary source and is recommended in the absence of any recent primary source where inputs are elicited for a DME population.	Sample size < 100	Canada
Abell, R	Wider vision-related disorders (Cataract patients)	Utility for complications related to cataract surgery.	Utility reported for before and after cataract surgery.	Utility not provided specific to cataract but cataract related issues, the detail is not included within the scope	Australia

Reference	DME / Other Retinal disorders / Wider vision-related disorders	Usable Input	Advantage	Disadvantage	Country
				of the model.	
Black, N	Wider vision-related disorders (Cataract)	Change in EQ-5D before / after surgery	Utility value reported for varying VA reported before and after surgery.	Utility value provided in a format not usable within the current scope of the model.	UK
Blackhouse, G	Wider vision-related disorders (Cataract)	Utility associated with development of cataract before / after surgery	Utility value reported for varying VA reported before and after surgery.	Utility value provided in a format not usable within the current scope of the model.	Canada
Buchholz, P	Wider vision-related disorders (Patients with moderate-to-severe dry eye)	SG / TTO Utility value for Monocular / Binocular Blindness	Utility reported for different levels of blindness based on the number of eyes affected.	Sample size < 100	UK
Clark, A	Wider vision-related disorders (Post-Operative Endophthalmitis)	EQ-5D for Endophthalmitis	Utility value specific to adverse event of interest in the Australian model reported.	Sample size < 100	Australia
Chia, E-M	Wider vision-related disorders (Non-correctable unilateral visual impairment)	SF-36 Summary score for cataract.	HRQOL for cataract patients elicited from a large multicentre patient population.	SF-36 values will need to be converted to single utility values.	Australia
Conner-Spady, BL	Wider vision-related disorders (Cataract)	EQ-5D for first eye /second eye surgery	Utility value presented for different types of cataract surgery. Article recommended as it is the more recent compared to Conner-Spady, BL[145]	Results may not be generalisable, as patients and surgeons included in the study were those who were willing to participate.	Canada
Conner-Spady, BL	Wider vision-related disorders (Cataract)	EQ-5D of cataract patients	Utility value presented for different types of cataract surgery.	Results may not be generalisable, as patients and surgeons included in the study were those who were willing to participate.	Canada

C2. **Priority question: Page 268** (of the company submission)**.** Given the inclusion of body mass index (BMI) in the regression equation for health-related quality of life, it appears that a number of functional forms were explored before a decision was made to use the functional form. Please outline all the functional forms that were explored, the coefficients and summary statistics of these functional forms and the rationale for choosing the form adopted.

Body mass index was included because it had been shown to have a statistically significant impact on quality of life in diabetic patients. A commonly cited study showing this is Bagust et al 2005[3]. The identity functional form was chosen based on the outputs of the "gladder" command in Stata which tests multiple functional forms of the variable in question for normality and therefore compliance with the assumptions of linear regression. The results showed that BMI could be considered normal ($p<0.000$) and therefore other transformations were not included in the regression model. In addition, the coefficient produced was similar in magnitude to the coefficient produced by Bagust et al.

C3. **Page 288. Section 7.6.1** (of the company submission)**.** Bullet point 5 refers to the "ERG suggested relative risk of mortality". Please clarify what this means.

In the ERG's (Aberdeen HTA Group) comments on the post referral decision meeting for Aflibercept for treating diabetic macular oedema on the 26th August 2014 it stated:

The ranibizumab submission for DMO highlighted two papers giving a relative risk of mortality for diabetics with DMO compared to diabetics and for diabetics compared to the general population. It would be expected that these would at a minimum inform a sensitivity analysis.

Given this request a relative risk of death based on the ranibizumab submission was included as a scenario analysis. A relative risk of 1.27 from the ranibizumab submission (Table B24) was applied to the risk of mortality of patients with diabetes to represent the increased likelihood of death in a patient with DMO. In the scenario analysis described in the aflibercept submission the overall relative risk of death applied for DMO patients was 2.45 applied: 1.27 for DMO patients versus non-DMO patients multiplied by 1.93 for diabetics vs. non-diabetics.

C4. **Pages 321-338. Tables 111, 113, 114, 116, 118, 121, 126** (of the company submission). The tables listed in this section show the comparator technologies as dominant over aflibercept. Should this be the other way round? If so, please amend the table to make it clearer.

The tables have been added below with the original table numbers:

Table 111: Results of the scenario analysis using EQ-5D utilities from VIVID/VISTA

[3] Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data 26. Health Econ 2005 Mar;14(3):217-30.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.398	9.052				
Ranibizumab		11.386	9.035	-8,911	0.014	0.0168	Aflibercept is dominant
Laser		11.339	8.901	-2,438	0.059	0.1504	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 113: Results of the scenario analysis using Brown 1999 utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]		8.738				
Ranibizumab			8.648	-8,911	0.014	0.0892	Aflibercept is dominant
Laser			8.346	-2,438	0.059	0.3919	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 114: Results of the scenario assuming ranibizumab and aflibercept require equivalent monitoring

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.398	7.690				
Ranibizumab		11.386	7.598	-8,365	0.014	0.0919	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 116: Results of the scenario analysis where the ERG's suggested relative risk of mortality was used

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]		7.199				
Ranibizumab			7.122	-8,626	0.000	0.0768	Aflibercept is dominant
Laser			6.870	-1,505	-0.006	0.330	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 118: Results of the scenario analysis comparing aflibercept with dexamethasone intravitreal implant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.398	7.552				
Dexamethasone		11.346	7.232	-9,888	0.052	0.320	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 121: Results of the exploratory analysis comparing aflibercept with fluocinolone acetonide intravitreal implant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.399	7.566				
Fluocinolone		11.345	7.295	-12,414	0.054	0.271	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 126: Results of the explanatory analysis comparing aflibercept with fluocinolone in pseudophakes

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.402	7.596				
Fluocinolone		11.342	7.278	-13,662	0.060	0.318	Aflibercept is dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

C5. It seems likely that body mass index (BMI), best corrected visual acuity (BCVA) in the best seeing eye (BSE) and BCVA of the worst seeing eye (WSE) may be positively correlated with the other complications of diabetes. These will all have an impact upon quality of life, but the analysis is restricted to BMI, BCVA BSE and BCVA WSE only. This could argue for a repeated measures analysis. Please clarify why this approach was not considered?

Repeated measures analyses were included in the utility analysis but added little extra predictive power when compared with the ordinary least squares. In addition, the regression coefficients generated by the repeated measures analyses were not dissimilar to those generated by the OLS. The results of OLS, fixed effects, random effects and generalised estimating equations models are presented below.

- **Ordinary least squares regression**

A complete case analysis approach resulted in regression model being made on [redacted] observations for the two-eye model. The regression equation was:

$$y_i = \boldsymbol{\alpha} + \boldsymbol{\beta_1}\,(\text{log of BCVA of BSE}) + \boldsymbol{\beta_2}\,(\text{log of BCVA of WSE}) + \boldsymbol{\beta_3}\,(\text{age}) + \boldsymbol{\beta_4}\,(\text{baseline BMI}) + u_i$$

The results indicated that there is a positive relationship between BCVA of the WSE and BSE and utilities. This multivariate analysis, in which both the BSE and WSE were considered simultaneously, suggests that BSE BCVA had higher impact on the utility than WSE. In terms of the covariates included in the model, age and baseline BMI had a negative impact on predicted utility. These values were small but statistically significant. Patient's visit time was found to be non-significant and so, not

included in the model. Mean estimates of regression coefficients and uncertainty in these estimates are shown in
Table **C5.1** below for the two-eye model.

Table C5.1: Ordinary least squares regression for two-eye model

	Coefficients	SE	P-values
log(BCVA of BSE)	[redacted]		
log (BCVA of WSE)			
Age			
Baseline BMI			
Constant			

For this model, R-squared = 0.0523 and RMSE = 0.21951.The variance-covariance matrix is given below (Table C5.2).

Table C5.2: Variance-covariance matrix for OLS regression for two-eye model

	log(BCVA of BSE)	log (BCVA of WSE)	Age	Baseline BMI	Constant
log(BCVA of BSE)	[redacted]				
log (BCVA of WSE)					
Age					
Baseline BMI					
Constant					

a. Random effects model

In order to account for the panel aspect of the dataset, random and fixed effects models were considered. Results from Hausman test suggested that a random effects model be used (p-value of the test was 0.1646). 2321 observations in a random effects model resulted in overall R-square of 0.0516 (within model R-square is 0.0023 and between model R-square is 0.0687) for the two-eye model. The mean estimates of regression coefficients and uncertainty in these estimates including variance-covariance matrix are shown in Table C5.3 and Table C5.4 below.

Table C5.3: Random effects model for two-eye model

	Coefficients	SE	P-values
log(BCVA of BSE)	[redacted]		
log (BCVA of WSE)			
Age			
Baseline BMI			
Constant			

Table C5.4: Variance-covariance matrix for random effects model for two-eye model

	log(BCVA of BSE)	log (BCVA of WSE)	Age	Baseline BMI	Constant
log(BCVA of BSE)	[redacted]				
log (BCVA of WSE)					
Age					
Baseline BMI					
Constant					

b. Generalized estimating equation model

2321 observations in a GEE model resulted in Wald χ^2 of 51.94 and corresponding p-value of <0.001 suggesting a good overall fit for the two-eye model. The mean estimates of regression coefficients and uncertainty in these estimates including variance-covariance matrix are shown in Table C5.5 and Table C5.6 below.

Table C5.5: Generalized estimating equation model for two-eye model

	Coefficients	SE	P-values
log(BCVA of BSE)	[redacted]		
log (BCVA of WSE)			
Age			
Baseline BMI			
Constant			

Table C5.6: Variance-covariance matrix for GEE model for two-eye model

	log(BCVA of BSE)	log (BCVA of WSE)	Age	Baseline BMI	Constant
log(BCVA of BSE)	[redacted]				
log (BCVA of WSE)					
Age					
Baseline BMI					
Constant					

c. Predicted utilities

Table 14 shows the utilities based on the 8-level classification. Note here that the predicted utilities differ slightly across OLS, random effects and GEE models (Table C5.7 -Table C5.9).

Table C5.7: Predicted utilities (8-level BCVA) from OLS regression model for two-eye model

BSE	WSE							
	>85	85-76	75-66	65-56	55-46	45-36	35-26	<26
>85	[redacted]							
85-76								
75-66								
65-56								
55-46								
45-36								
35-26								
<26								

Table C5.8: Predicted utilities (8-level BCVA) from random effects model for two-eye model

BSE	WSE							
	>85	85-76	75-66	65-56	55-46	45-36	35-26	<26
>85	[redacted]							
85-76								
75-66								
65-56								
55-46								

45-36	[redacted]
35-26	
<26	

Table C5.9: Predicted utilities (8-level BCVA) from GEE model for two-eye model

BSE	WSE							
	>85	85-76	75-66	65-56	55-46	45-36	35-26	<26
>85	[redacted]							
85-76								
75-66								
65-56								
55-46								
45-36								
35-26								
<26								

C6. **Priority question: Page 255**. **Table 71** (of the company submission)**.** This table appears to be the key input table for the economic modelling. No detail has been presented about how the values have been calculated within the submission. Based on cells K159:N169 of the CRT-SHIFT worksheet it appears that it is based on the proportions transitioning between baseline and week 52, with this then being adjusted along the lines of ((1+K169)^(1/12))-1.

- Please confirm that this is the method that has been used. If not, please clarify which method has been used.

The formula presented above is correct. The number of events over year was converted to an annual rate which was subsequently converted to a monthly rate using the formula described above.

Table C6.1: Number of patients gaining and losing letters over 12 months in the laser arm of the VIVID/VISTA studies

	Number of events	N	Annual rate	Monthly rate
Gain 10	64	286	0.223776	0.017
Lose 10	[redacted]			
Gain 15	24	286	0.083916	0.007
Lose 15	28	286	0.097902	0.008

- Please provide the corollary of cells B159:B167 and B327:I335 of the CRT-SHIFT worksheet for all patient populations so that the values in Table71 and cells X13:AS27 of the Tx_Input worksheet can be cross checked.

The table below is the 52 week shift table for all patients in the laser arms of the VIVD and VISTA studies:

Table C6.2: 52 week shift table for all patients in the laser arms of the VIVD and VISTA studies

Visual acuity level at Baseline	Visual acuity level at Week 52							
	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7	Level 8
Level 1	0	0	0	0	0	0	0	0
Level 2	0	0	0	0	0	1	0	0
Level 3	6	31	35	21	11	5	0	0
Level 4	0	9	34	38	13	4	0	1
Level 5	0	2	8	13	14	6	3	1
Level 6	0	1	0	2	7	5	3	1
Level 7	0	0	0	0	0	1	4	5
Level 8	0	0	0	0	0	0	0	1

LOCF: Last observation carried forward: Missing values and values observed after additional treatment were replaced by the last observed post baseline values prior to the missing value or the additional treatment.

The table below is the 52 week shift table for patients with a CRT<400µm in the laser arms of the VIVD and VISTA studies:

Table C6.3: 52 week shift table for all patients in the CRT <400µm subgroup in the laser arms of the VIVD and VISTA studies

Visual acuity level at Baseline	Visual acuity level at Week 52							
	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7	Level 8
Level 1	[redacted]							
Level 2								
Level 3								
Level 4								
Level 5								
Level 6								
Level 7								
Level 8								

C7. **Priority question:** Please provide the corollary of cells B4:I335 of the *CRT-SHIFT* worksheet for the subgroup of patients with central retinal thickness (CRT) thickness < 400µm.

These are presented in a separate Excel file that is academic in confidence.

C8. **Page 255. Table 71** (of the company submission). Please provide the information in table 71 separately for the VISTA trial and the VIVID trial.

The annual probability of gaining and losing letters based on the VIVID and VISTA trials is presented below.

Table C8: Annual probability of gaining and losing letters based on the VIVID and VISTA

	Monthly transition probability		
	VIVID/VISTA	**VIVID**	**VISTA**
Gain 10 letters	0.01697	0.01928	0.01494
Lose 10 letters	[redacted]		
Gain 15 letters	0.00674	0.00728	0.00627
Lose 15 letters	0.00781	0.00844	0.00728

C9. **Priority question: Page 255. Table 71** (of the company submission)**.** Please provide table 71 split by central retinal thickness (CRT) ≥ 400 µm and CRT thickness < 400 µm.

The annual probability of gaining and losing letters based on the VIVID and VISTA trials is presented below.

Table C9: Annual probability of gaining and losing letters based on the VIVID and VISTA

	Monthly transition probability		
	Whole population	**CRT ≥400**	**CRT <400**
Gain 10 letters	0.01697	[redacted]	
Lose 10 letters	[redacted]		
Gain 15 letters	0.00674		
Lose 15 letters	0.00781		

C10. **Priority question:** It is not clear how to run the model to replicate the results for the subgroup with CRT thickness ≥ 400 µm of Tables 124 and 125 of the submission. Please explain how these results were generated.

In order to replicate results for the subgroup with CRT ≥400 of tables 124 and 125 of the submission the source of laser efficacy in the executive summary tab has to be changed to subgroup.

C11. Within the Markov-Laser worksheet there is a drop down 'Yes/No' option located around the AL82 cell location. The corollary of this does not seem to appear in the other Markov worksheets. Please clarify the function of this drop down and which cells are directly affected by it.

The drop down "Yes/No" in the Markov-Laser worksheet has the same function of the drop down "Yes/No" located in the executive summary tab regarding the use of the shift tables. This may be deleted as it was used as test when the model was built.

Section D: Textual clarifications and additional points

D1. **Pages 72-96. Figures 9, 10, 13, 14, and 15** (of the company submission). The text in these figures is difficult to read because of the small size. Please provide enlarged text.

These figures had been pasted from the trial report in a way that minimised the file size (megabytes) of the entire document. This affected the quality of the font when the figure is enlarged. We have pasted the figures below in picture format to give clarity. The figure labels have been included as per the original submission but amended as requested.

Figure 9 (of original submission): Mean change from baseline in BCVA in ETDRS letter score at week 52 for the integrated analysis of the VISTA and VIVID studies [FAS;LOCF] (27)

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

[FIGURE DELETED]

Figure 10a): Pre-specified subgroup analysis of change in BCVA from baseline to week 52 (Integrated analysis; FAS; LOCF) (27) – 2Q4 versus laser

[FIGURE DELETED]

Figure 10b): Pre-specified subgroup analysis of change in BCVA from baseline to week 52 (Integrated analysis; FAS; LOCF) (27) – 2Q8 versus laser

[FIGURE DELETED]

Figure 13 (of original submission): Analysis of primary endpoint by baseline VA category subgroups (integrated data from VISTA and VIVID studies)(FAS; LOCF) (Pre-specified analysis)

[FIGURE DELETED]

Figure 14 (of original submission): Analysis of secondary endpoint - proportion of patients gaining ≥10 letters from baseline at week 52 - by baseline VA category subgroups (integrated data from VISTA and VIVID studies)(FAS; LOCF) (Pre-specified analysis)

[FIGURE DELETED]

Figure 15 (of original submission): Analysis of secondary endpoint - proportion of patients gaining ≥15 letters from baseline at week 52 - by baseline VA category subgroups (integrated data from VISTA and VIVID studies)(FAS; LOCF) (Pre-specified analysis)

[FIGURE DELETED]

D2. **Page 77** (of the company submission)**.** The figure at the top of the page does not have a figure number or title. Please clarify what this figure relates to and add a figure number and title.

This is the second part of Figure 10: Pre-specified subgroup analysis of change in BCVA from baseline to week 52 (Integrated analysis; FAS; LOCF). The first part refers to 2Q4 and the second part refers to 2Q8, as stated beneath the horizontal axis. The auto-formatting of the document shifted the second part onto the next page. This has been included as part a) and b) in the response to the above question D1 to add clarity.

D3. **Pages 197 and 337** (of the company submission). Please correct the referencing error in the text.

On page 197, the cross reference is Table 58 as stated in the text. The cross-referencing system has added an error message but this can be ignored. On page 337, the error message should be replaced with reference to the Table 125 below.

D4. **Pages 310, 320 and 322** (of the company submission). The tables on these pages do not have numbers or titles. Please clarify what these tables relate to and add a table number and title?

The table on page 310 is Table 301 that has run over from page 309**.**

Page 320: Comparison of aflibercept and laser based on observed efficacy data from the VIVID/VISTA trials

Efficacy data based on the direct comparison between aflibercept and laser were obtained from the VIVID/VISTA trials. Different probabilities of gaining or losing letters were applied at each cycle during the first year. The results of this scenario analysis showed that compared to laser, aflibercept was associated with higher LYs (incremental LYs: 0.0699), QALYs (incremental QALYs: 0.4100) and lower costs (incremental costs: -£5,937). Compared to laser, aflibercept was deemed cost-effective in the treatment of DMO (ICER:£ -£14,481).

Table 109(b): Cost effectiveness results using observed efficacy data from the VIVID/VISTA trials

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.329	7.606				
Laser		11.259	7.196	-5,937	0.0699	0.4100	Aflibercept Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Page 322: Brown 1999 utilities

In this scenario utility values derived from Brown 1999 (75) were applied. Utilities derived from Brown et al present a small range between the best and the worse utility values. Utility values used in this scenario are reported in Table 112(a).

Table 112(a): Utilities based on Brown 1999

		Better seeing eye							
		VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8
Worse seeing eye	VA1	0.84							
	VA2	0.84	0.84						
	VA3	0.83	0.83	0.78					
	VA4	0.83	0.83	0.78	0.78				
	VA5	0.81	0.81	0.77	0.77	0.73			
	VA6	0.80	0.80	0.76	0.76	0.72	0.68		
	VA7	0.79	0.79	0.75	0.75	0.71	0.67	0.63	
	VA8	0.78	0.78	0.74	0.74	0.70	0.66	0.62	0.58

As expected, replacing the utility values used in the base case impacted incremental QALYs only.

Table 112(b): Cost effectiveness results using utilities based on Brown 1999

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]						
Ranibizumab				-8,911	0.014	0.0306	Aflibercept Dominant
Laser				-2,438	0.059	0.1960	Aflibercept Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Brown 2000 utilities

Utilities derived from Brown 2000 (84) were used in this scenario analysis. As for Brown 1999(75), utilities values are concentrated in a smaller range between best and worst utility values when compared to Czosky-Murray (76) (Table 83).

Table 113(a): Brown 1999 utilities by health state

		Better seeing eye							
		VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8
Worse seeing eye	VA1	0.89							
	VA2	0.89	0.89						
	VA3	0.87	0.87	0.81					
	VA4	0.84	0.84	0.78	0.69				
	VA5	0.81	0.81	0.75	0.66	0.56			

		Better seeing eye							
		VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8
	VA6	0.81	0.81	0.75	0.66	0.56	0.55		
	VA7	0.80	0.80	0.74	0.65	0.55	0.54	0.52	
	VA8	0.79	0.79	0.73	0.64	0.54	0.53	0.51	0.46

Aflibercept is still dominant when compared to both ranibizumab and laser since change in the utilities source only has an impact on the final QALYs. Results of this scenario are presented in Table 113(b) below.

Table 113(b): Results of the scenario analysis using Brown 1999 utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]		8.738				
Ranibizumab			8.648	-8,911	0.014	0.0892	Aflibercept Dominant
Laser			8.346	-2,438	0.059	0.3919	Aflibercept Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

D5. **Page 331** (of the company submission)**.** The text discussing the time horizon in the model is not clear. Please clarify if this is 1 year or 10 years.

The base case time horizon is 15 years as included in the main text on page 240 describing the model. This text is stating that scenarios with a time horizon of 10 years or less have higher incremental costs.

D6. **Page 334. Figure 76** (of the company submission)**.** The bottom figure does not have a title or number. Please clarify what this figure relates to and add a figure number and title. In addition both figures are small and it is difficult to read the text contained in them. Please provide clearer versions of these figures.

Figure 76a): Comparison of the visual acuity subgroups in RESTORE, VIVID and VISTA – 'Good vision' subgroup

[FIGURE DELETED]

*P<0.0001 vs. laser; †Adapted from Mitchell P et al 2011, final BCVA is estimated from the curve. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; RBZ, ranibizumab.

1. Bayer HealthCare Data on File. 2. Mitchell P et al. Ophthalmology 2011; 118 (4): 615–6

Figure 76b): Comparison of the visual acuity subgroups in RESTORE, VIVID and VISTA – 'Poor vision' subgroup

[FIGURE DELETED]

*P<0.0001 vs. laser; †Adapted from Mitchell P et al 2011, final BCVA is estimated from the curve. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; RBZ, ranibizumab.

1. Bayer HealthCare Data on File. 2. Mitchell P et al. Ophthalmology 2011; 118 (4): 615–625.

D7. **Page 335. Table 122** (of the company submission)**.** There is a table and a figure which do not have a number or title. Please clarify what they relate to and add table and figure numbers and titles.

Table 122: Mean average change in best-corrected visual acuity letter score from baseline to week 52 – subgroup analysis (FAS, LOCF)

Table 122 a) Mean average change in best-corrected visual acuity letter score from baseline to week 52 – subgroup analysis from VISTA and VIVID (data on file)

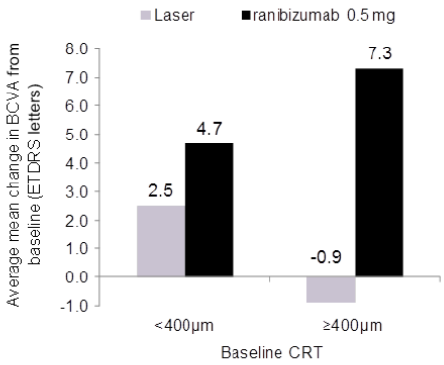
Population	Treatment group	Number of patients	Mean change (SD)
Baseline CRT <400µm	VTE 2Q4	[redacted]	
	VTE 2Q8		
	Laser		

Population	Treatment group	Number of patients	Mean change (SD)
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	
	VTE 2Q8		
	Laser		

Table 122 b) Mean average change in best-corrected visual acuity letter score from baseline to week 52 – subgroup analysis from RESTORE (Mitchell 2011(31)):

	Ranibizumab	Ranibizumab 0.5mg +Laser	Laser
CRT (µm) <300	3.0 (N=19)	3.0 (N=20)	1.7 (N=21)
CRT (µm) 300-400	5.7 (N=32)	6.6 (N=37)	3.0 (N=34)
CRT (µm) >400	7.3 (N=62)	6.1 (N=59)	-0.9 (N=53)

TA122c) Average mean change in BCVA from baseline to M1-12, by CRT at baseline as taken directly from NICE TA274 manufacturer's submission (ETDRS letters)



n	55	52		54	62
Mean BCVA at baseline	66	69		59	61

D8. **Page 431 (of the company submission**). This page is left blank. Please confirm that this was intentional.

No, this was not intentional. There was an extra carriage return.

APPENDIX A – INCLUDED AND EXCLUDED STUDIES EXTRACTED FROM THE SYSTEMATIC REVIEW OF CLINICAL STUDIES

Table 1: All included DME studies and records with key study characteristics (clinical effectiveness)

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
EUCTR2010-022364-12-DE [14] NCT01331681 [15] Clinical study report[16] Korobelnik, 2014[17] Nguyen, 2014[18] Lorenz, 2014[19] Brown, 2014[20]	2Q4 AFB + sham laser (n=136) 2Q4 then 2Q8 AFB+ sham laser (n=135) Sham+ macular laser (n=133)	VIVID-DME	12	Fixed	2 mg every 4 weeks, or every 8 weeks (following 5 monthly doses).	Yes
Schmidt-Erfurth U, 2013 [21A] NCT01363440[22] Clinical study report[23] Korobelnik, 2014[17] Nguyen, 2014[18] Lorenz, 2014[19] Brown, 2014[20] 24m Key results memo [24]	2Q4 AFB + sham laser (n=156) 2Q4 then 2Q8 AFB+ sham laser (n=154) Sham+ macular laser (n=156)	VISTA-DME	12 24	Fixed	2 mg every 4 weeks, or every 8 weeks (following 5 monthly doses).	Yes
Lam, 2009* [25] Lai, 2008[A] [26]	1.25mg BVZ (n=26) 2.5mg BVZ (n=25)	Lam 2009	3,6 6	fixed fixed	3x monthly injections	Yes but does not form a closed network.
Lim, 2012* [27] NCT01342159 [28]	1.25 mg BVZ + 2 mg IVTA (n=36) 1.25 mg BVZ (n=38) 2 mg IVTA (n=37)	NCT01342159	3, 6, 12	Fixed then PRN Fixed then PRN Fixed then PRN	For the BVZ group: 2x at 6-week intervals intravitreally. BVZ PRN according to CMT – BVZ given to IVTA arm.	Yes
Shoeibi, 2013* [29] Ahmadieh, 2008[30] NCT00370422 [31]	1.25mg BVZ + 2mg IVTA (n=37) 1.25 mg BVZ (n=41) Sham (n=37)	NCT00370422	3, 4, 6, 9	Fixed then PRN Fixed then PRN Fixed	3 consecutive injections at 6 week intervals. Second and third injections in the BVZ + TA group were with BVZ only. BVZ PRN according to CMT and VA	Yes
Prager, 2010* [32] NCT00682539 [33] Kriechbaum, 2014 [34]	2.5mg BVZ (n=15) 8mg IVTA/sham (n=15)	Triastin NCT00682539	6	Fixed/PRN	3x monthly BVZ 1x IVTA then 2 x sham Reinjection based on OCT	Yes, but does not form a closed network.

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
					measurements of CRT and VA	
ATEMD Andrade, 2010[A 35] NCT00737971 [36]	1.25 mg BVZ + 4mg IVTA (n=9) 1.25 mg BVZ (n=3), 4mg IVTA (n=6) Total =65 randomised	Andrade 2010	6	fixed	Monthly injections.	No. Abstract with insufficient data for analysis (no baseline data and VA reported as 'lines').
Galassi, 2011[A 37] Katayama, 2010 [A 38] Almeida, 2011 [A39] NCT00997191 [40]	1.5mg BVZ + laser (n=21) 4mg IVTA + laser (n=20) FG macular laser (n=23)	IBETA NCT00997191	12	Fixed then PRN Fixed then PRN (Fixed then PRN)	Retreatment at weeks 20 and 40 according to central macular thickness. Unclear if laser is given PRN.	Yes
Pappas, 2008 [A 41]	1.25mg BVZ (n=27) 4mg IVTA + FG or modified grid laser PC (n=35)	Pappas 2008	6	Fixed then PRN	Unclear. Appears to be single injection and then PRN.	Yes
Azad, 2012* [42]	1.25mg BVZ (n=20), 4mg IVTA (n=20) mETDRS macular grid laser (n=20)	Azad 2012	3, 6	Fixed then PRN Fixed then PRN (Fixed then PRN)	Single treatment and then PRN. In each group, eyes with a 2 line decrease in the BCVA from the baseline, increasing leakage on FFA or a 100 µ increase in the CMT on OCT were retreated according to the treatment regimen as outlined above for the respective group.	Yes
Rajendram, 2012 [43]* Fraser-Bell, 2011 [A 44] Michaelides, 2010 [45] Michaelides, 2010 [46] Hykin, 2010 [A 47] Hamilton, 2010 [A 48] EUCTR2007-000847-89-GB [49] ISRCTN41984498 [50]	1.25mg BVZ (n=42) mEDTRS MLT laser (n=38)	BOLT	4, 12, 24	Fixed then PRN (PRN)	BVZ= injection at baseline, 6 and 12 weeks. Retreatment according to OCT.	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Chakrabarti, 2008 [A 51]	1.25 mg BVZ + 4 mg IVTA +focal laser (n= 20) 1.25mg BVZ +focal laser (n=20); 4mg IVTA +focal laser (n= 20);	Chakrabarti 2008	NR	NR	unclear	No. Insufficient information in poster (unclear reporting of data, units to measure VA not given).
Solaiman, 2012 [A 52]	BVZ+ macular grid PC (n=16) BVZ n=16	Solaiman 2012	Unclear	PRN	unclear	No. Dose NR
Solaiman, 2010*[53]	1.25mg BVZ (n=21), 1.25mg BVZ + modified grid laser PC (n=22) modified grid laser PC (n=19)	Solaiman 2010	6	fixed	Single injections of BVZ.	No. Single injection of BVZ
Soheilian, 2012[54] Soheilian, 2007[55] Soheilian, 2011[56] Soheilian, 2009* [57] NCT00370669 [58]	1.25 mg BVZ + sham laser (n=50), 1.25 mg BVZ+ 2 mg IVTA + sham laser (n=50) FG macular PC + sham injection (n=50)	NCT00370669	3, 6, 9, 12, 18, 24	Fixed then PRN Fixed then PRN (Fixed then PRN)	Single treatment then PRN. Retreatment was performed based on persistence of clinically significant macular oedema. Retreatments were carried out at 12-week intervals as required.	Yes
Faghihi, 2008* [59]	1.25mg BVZ + 2mg IVTA n=41 1.25mg BVZ n=42 ETDRS laser n=47	Faghihi 2008	4	Fixed then PRN Fixed then PRN (Fixed then PRN)	Single treatment then PRN. In case of persistent macular oedema (thickening of CRT >250 µm, leakage from the perifoveal capillary vessels on FA; > 16 weeks following any of the procedures), retreatment was performed.	Yes
Leitao, 2010[A 60]	1.25mg BVZ+ 40mg/ml subtenonian triamcinolone (n=NR) 1.25mg BVZ (n=NR); total = 24	Leitao 2010	3,6	NR	NR	No. Insufficient information in abstract (unclear n per treatment arm, no baseline).
Takamura, 2014[61]	1.25mg BVZ + grid/focal laser (n=26)	Takamura 2014	6	Fixed	Single treatment of BVZ plus grid/focal laser, followed by	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
	1.25mg BVZ + grid/focal laser + Targeted Retinal Photocoagulation(n=26)				TRP laser or not.	
Hurtado, 2012 [A 62]	0.5 RBZ (n=32), 0.5 RBZ + 2mg IVTA (n=20) macular laser PC (n=28)	Hurtado 2012	3	Unclear	unclear	No. Unclear quantitative data.
Prunte, 2013[A 63] NCT01171976 [64] EUCTR2010-019795-74-BE [65]	0.5mg RBZ TE + laser (n=121) 0.5mg RBZ TE(n=128) 0.5mg PRN RBZ (n=123)	RETAIN NCT1171976	baseline	TE and PRN	PRN treatment based on disease activity with monthly monitoring. Treat-and-extend (TE) provides treatment at any follow-up visit but increases interval to next visit in case of stable vision.	No follow-up data
Nguyen, 2012 [66] Brown, 2013 [67] NCT00473382 [68] Brown, 2012 [A 69] Boyer, 2011 [A 70] Do, 2012 [A 71] Ehrlich, 2012 [A 72] Kitchens, 2012 [A 73] Ip, 2013 [A 74] Morse, 2013 [A 75] Ip, 2012 [A 76] Brown, 2011 [A 77] NCT00473330 [78] Rohit, 2012 [A 79] Mieler, 2013[A 80] Sophie, 2014 [81]	0.3mg RBZ + deferred laser (n= 125), 0.5mg RBZ + deferred laser (n=127) Laser + Sham injection (n=130)	RIDE NCT00473382	24	Fixed Fixed (Fixed)	Monthly injections. All patients were eligible for laser treatment from month 3 based on prespecified subjective and objective criteria (very few actually received laser <2%, therefore not considered a combination treatment in network).	Yes
	0.3mg RBZ + deferred laser (n=125), 0.5mg RBZ + deferred laser (n=125) Laser + Sham injection (RISE n=127)	RISE NCT00473330	24	Fixed Fixed (Fixed)	Monthly injections. All patients were eligible for laser treatment from month 3 based on prespecified subjective and objective criteria (very few actually received laser <2%, therefore not considered a combination treatment in network).	Yes
Novartis 2013 [82] EUCTR2007-004877-24-FR [83] RESTORE Extension EUCTR2008-007467-17-FR [84]	0.5mg RBZ plus sham laser (n = 116) 0.5 mg RBZ plus laser (n = 118) sham injections plus laser (n =	RESTORE NCT00687804	12, 24, 36	Fixed then PRN Fixed then PRN	3 monthly injections were followed by 'as needed' using pre-specified criteria (primarily VA).	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Mitchell, 2011*[85] Mitchell, 2010[A 86] Massinon, 2010 [A 87] Mitchell, 2013 [88] Mitchell, 2012 [A 89] Mitchell, 2010 [A 90] Mitchell, 2011 [A 91] Schlingemann, 2010 [A 92] Bandello, 2011 [A 93] Mitchell, 2013 [A 94] Mitchell, 2011 [A 95] Lang, 2012 [A 96] Mitchell, 2012 [A 97] Boiadera, 2013 [A 98] Lang, 2012 [A 99] Lanzetta, 2012 [A 100] Mitchell, 2012 [A 101] Schmidt-Erfuth, 2014[102] Gerendas, 2014[103] Margaron, 2014[104]	111) 0.5mg RBZ + laser (n=74) 0.5mg RBZ + laser (n=83) 0.5mg RBZ + laser (n=83)	RESTORE EXT		(Fixed then PRN)	Randomised groups from the core 12m study were preserved in the extension study. In the extension study all patients could receive 0.5mg RBZ PRN monthly up to a maximum of 24 injections in the extension study phase. Laser treatment could be given as required. Decisions on laser treatment were independent of decisions to inject ranibizumab.	
Koh, 2012 [105 A] NCT00989989 [106] Ohji, 2012 [107 A]	0.5mg RBZ+sham laser (n=133) 0.5mg RBZ + laser (n=132) Sham injection+laser (n=131	REVEAL/ NCT00989989	12	Fixed then PRN Fixed then PRN (Fixed then PRN)	3 monthly injections then PRN based on VA stability.	Yes
Ristau, 2013 [108 A] NCT01131585 [109]	0.5 mg RBZ+ FG laser PC (n=85) FG laser PC+ sham injections (n=43)	RELATION	12	Fixed then PRN (Fixed then	4 monthly injections then PRN based on VA stability.	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Lohmann, 2013 [110A]				PRN)		
Varma, 2012 [79 A]		RISE/RIDE RESTORE				
Diabetic Retinopathy Clinical Research, Network. http://drcrnet.jaeb.org/Studies.aspx Elman, 2012[111]* Elman, 2011[112] Elman, 2010 [113] NCT00444600 [114] Berger, 2010 [A 115] Kim, 2012 [A 116]	0.5mg RBZ + prompt laser (n=187) 0.5mg RBZ + deferred laser (n=188) sham injection + prompt laser (n=293), 4 mg IVTA + prompt laser (n=186)	NCT00444600/ LRT for DME Protocol I	12, 24, 36	Fixed then PRN Fixed then PRN (Fixed then PRN) Fixed then PRN	RBZ= every 4 weeks for at least 4 doses; an additional dose was given at weeks 16 and 20 unless success criteria were met. Prompt (7 to 10 days after the initial RBZ injection) or was deferred for at least 24 weeks.	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Diabetic Retinopathy Clinical Research, Network. 2011 [117] NCT00445003 [118] Googe, 2011 [A 119] http://drcrnet.jaeb.org/Studies.aspx	0.5 mg RBZ + Focal/Grid/PRP Laser (n = 113) 4mg IVTA + Focal/Grid/ PRP Laser (n = 109) Sham + Focal/Grid/ PRP Laser (n = 123)	NCT00445003 LRT for DME for PRP Protocol J	3, 12	Fixed then PRN Fixed then PRN (Fixed then PRN)	The initial sham or intravitreal injection was given on the day of randomization. Second injection at the 4-week visit. Focal/grid laser performed 3 to 10 days after the injection for all treatment groups. Panretinal photocoagulation could be initiated immediately after the focal/grid laser or on a subsequent day but was to be initiated within 14 days of the baseline injection and fully completed within 49 days of randomization. After 14-wk visit, additional treatment given at the investigator's discretion.	Yes
Comyn, 2013 [A 120] Gohil, 2013 [A 121] NCT01223612 [122] Comyn, 2014* [123]	0.5 mg RBZ (n=NR) mETDRS laser (n=NR) total = 36	NCT01223612 LUCIDATE	3, 6, 9, 12	Fixed then PRN (Fixed then PRN)	3x 4 weekly injections, then PRN.	Yes.
Cserhati, 2013 [A 124]	RBZ (n=27), RBZ (fixed/PRN)+ navigated laser (n=15) RBZ (PRN)+ navigated laser (n=34)	Cserhati 2013	12	fixed/PRN and PRN		No. Abstract only: no dose
NCT00668239 [125] Gil, 2011* [126]	4mg IVTA + sham laser (n=7) pan laser PC + sham injection(=7)	NCT00668239	3, 6	Fixed (Fixed)		Yes, but does not form a closed network.
Meza-de Regil, 2004 [A 127]	Laser + 4mg IVTA (n=NR) 4mg IVTA (n=NR)	Meza 2004	3, 6	Fixed Fixed	Patients were randomized to receive a single injection of	No. Single treatment, no

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
	Total = 120				triamcinolone acetonide (4mg) through pars plana (group A) or same dose of triamcinolone and laser grid photocoagulation two weeks after injection (Group B).	PRN.
Mohamed, 2006 [A 128]	4mg IVTA + laser n=38 4mg IVTA n=41	Mohamed 2006	6	Fixed Fixed	NR	No. Single treatment, no PRN.
Kim, 2010 [A 129]	4mg IVTA + macular laser PC (n=37 completed, n=48 randomised) 4mg IVTA (n=26 completed, n=38 randomised)	Kim 2010	36	Fixed then PRN Fixed then PRN	unclear	Yes
Aydin, 2009 [130]	4mg IVTA + laser (n=17) Laser + 4 mg IVTA (n=13) 4mg IVTA (n=19)	Aydin 2009	3, 6	Fixed	IVTA was carried out 3 weeks before laser (group 1), immediately after macular laser photocoagulation (group 2). Group 3 received only IVTA application.	No. Single treatment, no PRN.
Mirshahi, 2010 [131]	4mg IVTA + PR PC + Macular PC (n=18) PR PC + Macular PC (n=18)	Mirshahi 2010	4, 6, 18	Fixed then PRN (Fixed then PRN)	IVTA injection 1 week before initial PRP and MPC (injected eye), and the other eye was treated with PRP and MPC (control eye). All patients received the same number of injections. PR PC was performed in three sessions at weekly intervals.	Yes
Lam, 2007 [132]	4mg IVTA + sequential grid laser (n=36) grid laser PC (n=37), 4mg of IVTA (n=38)	Lam 2007	4, 6	Fixed then PRN (Fixed then PRN) Fixed then PRN	In the event of persistence or recurrence of macular oedema, repeat treatments were offered to patients, according to the arms to which they were randomized, at intervals of no less than 4 months.	Yes
Diabetic Retinopathy Clinical	1mg IVTA (n=256)	DRCRN 2009	4,	Fixed then	Retreatment at 4 month	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Research, N. 2009 *[133] NCT00367133 [134] Diabetic Retinopathy Clinical Research, N. 2008 [135]	4mg IVTA (n=254) FG PC (n=330)	(IVT) NCT00367133	8, 12, 16, 20, 24, 36	PRN Fixed then PRN (Fixed then PRN)	intervals unless deferral criteria were met. Data presented	
Bordon, 2006[136]	8mg IVTA n=15 laser n=18	Bordon 2006	12	PRN	Treatment was repeated every 3 months if necessary	Yes, but does not form a closed network
Norlaili, 2011 [137]	Laser (n=20) 4mg IVTA (n=20)	Norlaili 2011 ISRCTN05040192	3	(Fixed) Fixed	Single treatment.	No. Single treatment, no PRN.
Ockrim, 2008 *[138] Ockrim, 2006 [A 139] Sivaprasad, 2008 [140]	4mg IVTA (n=43) ETDRS laser (n=45)	Ockrim 2008	4, 8, 12	Fixed then PRN (Fixed then PRN)	Patients were retreated at 4 and 8 months if they had persistent macular oedema on clinical examination with final review at 12 months.	Yes
Maia, 2009 [141]	4mg IVTA + PR PC + Macular FG PC (n=NR) Panretinal PR PC + Macular FG PC (n=NR); total n=22	NCT00443521	3, 6, 9, 12	Fixed (Fixed then PRN)	Additional macular (grid and/or focal) laser treatment was permitted if CSME and treatable lesions on FA were still present at any follow-up study visit.	Yes
Saraiva, 2008[142]	macular grid PC Laser + 4mg IVTA (n=) 4mg IVTA (n=) macular grid PC laser (n=) (total n=30)	Saraiva 2008	6	NR	NR	No. Number per treatment arm not reported. Outcomes not reported in full for extraction.
Gillies, 2010 [143]* Gillies, 2011[144] NCT00148265 [145] Gilles, 2009 [A 143]	mETDRS Laser + 4mg IVTA (n=42) mETDRS Laser + sham injection (n=42)	NCT00148265	6, 24	Fixed then PRN (Fixed)	Eyes assigned to IVTA received one injection Patients received laser treatment 6 weeks after injection. Retreatment with IVTA + laser was considered at the discretion of the chief investigator at each site at each visit.	Yes

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Gillies, 2006* [146] NCT00167518 [147] ACTRN12605000211662 [148] Gillies, 2005 [A 149] Gillies, 2010[150]	4mg IVTA n=34 saline placebo n=35 IVTA n=27 Sham n=25	TDMO NCT001675518 Post-hoc analysis	3, 24 36	Fixed then PRN Fixed (PRN)	Retreatment according to ETDRS. Laser also given PRN to placebo and IVTA	Yes
Diaz-Rohena, 2012[A 151] NCT01486238 [152]	Q4 pegaptanib (n=49) Q6 pegaptanib (n=23)	PRESERVE NCT01486238	6	fixed		Yes but does not form a closed network
Sultan, 2011* [153] NCT00605280 [154] Loftus, 2011 [155] Loftus, 2011 [A 156]	0.3mg pegaptanib (n=133) sham (n=127) 0.3mg PGT +laser (n=145) Sham +laser (n=143) 0.3mg pegaptanib (n=133) sham (n=127)	Macugen 1013 Study Group, NCT00605280	12, 24 24 12	yr. 1: fixed, yr. 2 PRN	Injections every 6 weeks (day 0 through week 48) for a total of 9 injections. At investigator determination (ETDRS criteria), laser PC could be performed at week 18.	Yes but does not form a closed network
NCT01100307 [157]	0.3mg peg. sham injection (n=243)	NCT01100307	3, 6, 12	Fixed	Every 6 weeks (q6)	Yes but does not form a closed network
Pearson, 2011* [158] Pearson, 2006 [A 159] Pearson, 2005 [A 160] NCT00502541 [161]	0.59mg FAc implant (n=127) Standard of Care; laser or observation(n=69)	NCT00502541	1.5, 3,6, 10, 12, 24, 36, 48	Fixed	Sustained release intravitreal implant releasing FA at 0.6µg/d decreasing over 1 month to 0.3-0.4 µg/d with a duration of 30 months. Laser PC was permitted post-implantation	Yes
Campochiaro, 2012 [162] Campochiaro, 2011 [163] Dempe, 2012 [A 164] NCT00344968 [165] Cunha-Vaz, 2014[166] Campochiaro, 2014 [A 167]	0.2µg/day FAc (n=376) 0.5µg/day FAc (n=395) Sham (n=185)	FAME	24, 36	Fixed then PRN	All patients were eligible for rescue laser therapy at investigator discretion after week 6 and could receive additional randomised study treatment after 12 months	Yes.
Pearson, 2004 [A 168] Pearson, 2003 [A 169] Pearson, 2002 [A 170]	2mg FAc implant (n=11) 0.5mg FAc implant (n=41) Standard of Care (n=28)	Pearson 2004	6, 12, 24	Unclear. Abstract only	Unclear. Abstract only	Yes.

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
	Standard of Care may include macular grid laser or observation					
NCT00490815[171]	0.2µg/day FAc (n=20) 0.5µg/day FAc (n=17)	NCT00490815	36	Fixed	Unclear. 0.5 µg/Day and 0.2 µg/Day Fluocinolone Acetonide Intravitreal Inserts.	Yes
Callanan, 2013 [172] NCT00464685 [173]	0.7mg dexamethasone implant + laser (n=126) Laser + sham injection (n=127)	PLACID	1, 4, 6, 9, 12	Fixed then PRN	Dex implant or sham treatment was performed at the baseline visit. One month later all patients were treated with modified ETDRS focal laser photocoagulation. Need for retreatment was assessed at months 4, 6 and 9. Patients could receive up to 3 additional laser treatments and 1 additional implant	Yes, but does not form a closed network.
Boyer, 2014 [174] Belfort, 2014 [A175] Danis, 2014 [A 176] Belfort, 2014 [A 177] Yoon, 2014 [A 178] NCT00168337[179] NCT00168389[180]	0.7mg dexamethasone implant (n=188) 0.35mg dexamethasone implant (n=181) Sham injection (n=185) 0.7mg dexamethasone implant (n=163) 0.35mg dexamethasone implant (n=166) Sham injection (n=165)	MEAD (NCT00168337) MEAD (NCT00168389)	36	Fixed then PRN	Study treatment was administered after all baseline evaluations. An applicator system was used to insert DEX implant into the vitreous of the study eye through the pars plana. In the sham procedure, a needleless applicator was pressed against the conjunctiva of the study eye	Yes.
Gillies, 2014 [A 181] NCT01298076[182]	Bevacizumab (n=42) Dexamethasone implant (n=46)	BEVORDEX	12	Unclear	Patients received bevacizumab 4 weekly or Ozurdex 4 monthly both pro re nata	No, dosages are unclear.
Williams, 2006[A183]	700µg dexamethasone drug delivery system (n=NR) 350µg dexamethasone drug delivery system (n=NR) Observation (n=NR)	Williams 2006	3	Unclear.	Unclear. Abstract only	Yes.
Haller, 2010*[184]	700µg dexamethasone implant	NCT00035906	1,	Fixed	Dexamethasone DDS was	Yes. Unclear if

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Haller, 2006 [A 185] NCT00035906 [186] Kupperman, 2005 [A 187] Kupperman, 2003 [A 188]	(n=57) 350µg dexamethasone implant (n=57) Observation (n=57)		2, 3, 6		surgically implanted into the vitreous cavity. Patients in the observation group received no study treatment and no sham procedure. Eyes that demonstrated VA loss ≥15 letters could be treated with other therapy including laser or IVTA	linked to Williams 2006.
Kuppermann, 2003 [A 189]	700µg dexamethasone implant 350µg dexamethasone implant Observation	Kuppermann 2003	3	Unclear. Abstract only	Unclear. Abstract only	Yes. Unclear if linked to NCT00035906.
Tewari, 1998 [190]	810nm diode laser 514nm argon laser	Tewari 1998	3,6	NE	NE	Yes but does not form a closed network
Akduman, 1997[191]	diode laser (810 nm) n=85 argon green laser (514 nm) n=86	Akduman 1997	15	NE	NE	Yes but does not form a closed network
Figueira, 2009* [192] ISRCTN90646644 [193] Khan, 2005 [A 194]	810nm micropulse diode laser (n=44) 514nm argon green laser (n=40)	MP1	12	NE	NE	Yes but does not form a closed network
Laursen, 2004 [195]	subthreshold micropulse diode laser (814 nm) n= 12 argon green laser (514 nm) n= 11	Laursen 2004a	6	NE	NE	Yes but does not form a closed network
Laursen, 2004 [A 196]	subthreshold micropulse diode laser (810nm) argon laser (514 nm)	Laursen 2004b	5	NE	NE	Yes but does not form a closed network
Grigorian, 2003 [A 197]	Subthreshold Micropulse Diode Laser n=10 Argon Laser n=10	Grigorian 2003	4	NE	NE	Yes but does not form a closed network
Lavinsky, 2011 [198] Cardillo, 2008 [A 199]	810nm ND-SDM laser (n=39), 810nm HD-SDM laser (n=42) 532nm mETDRS focal/grid laser (n=42)	NCT00552435	12	NE	NE	Yes but does not form a closed network
Vujosevic, 2010 [200]	810nm micropulse diode laser (n=32)	Vujosevic 2010	12	NE	NE	Yes but does not form a closed

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
	modified EDTRS 514nm laser (n=30)					network
Venkatesh, 2011 [201]	Subthreshold micropulse diode laser (n=23) Double frequency neodymium YAG laser (n=23)	Venkatesh 2011	6	NE	NE	Yes but does not form a closed network
Salman, 2011 [202]	Pascal laser (n=30) Conventional laser, macular PC (n=30)	Salman 2011	12	NE	NE	Yes but does not form a closed network
Blankenship, 1979 [203]	Argon laser PC (n=39) untreated (n=39)	Blankenship 1979	12, 24	NE	NE	Yes but does not form a closed network
Olk, 1986 [204]	modified grid argon blue/green laser 488,514nm (n=82) untreated (n=78)	Olk 1986	12, 24	NE	NE	Yes but does not form a closed network
Karacorlu, 1993[205]	Argon green laser 514nm PC (n=47) Dye Yellow laser 570nm PC (n=38)	Karacorlu 1993	12	NE	NE	Yes but does not form a closed network
Casswell, 1990[206]	krypton red laser 647nm (n=48) Argon green/blue laser 488/514nm (n=43)	Casswell 1990	24	NE	NE	Yes but does not form a closed network
Khairallah, 1996[207]	krypton red laser 647nm) n=72 argon green laser (514nm) n=79	Khairallah 1996	12	NE	NE	Yes but does not form a closed network
Zhou, 2008 [208]	krypton red laser 647nm) n=76 argon green laser (514nm) n=78	Zhou 2008	3-36	NE	NE	Yes but does not form a closed network
Olk, 1990 [209]	krypton red laser 647nm (n=109) Argon green/blue laser 514nm (n=116)	Olk 1990	12, 24	NE	NE	Yes but does not form a closed network
Fong, 2006 [A 210] DRCR.net	ETDRS laser n=92 mild macular grid (MMG) laser n=96	Fong 2006	12	NE	NE	Yes but does not form a closed network
Kumar, 2010 [211]	Subthreshold laser (n=15) Threshold laser (n=15)	Kumar 2010	4	NE	NE	Yes but does not form a closed network

Author Year Endnote	Intervention Comparator	Trial name/NCT	F-up (m)	Drug PRN or fixed (laser)	Detailed regimen	Included in primary network. Comments.
Shao, 2013 [212]	Subthreshold laser (n=27) Threshold laser (n=30)	Shao 2013	3	NE	NE	Yes but does not form a closed network
Patz, 1985 [213]	Deferred focal laser photocoagulation (n=1490) Immediate focal laser photocoagulation (n=754)	Patz 1985	12	NE	NE	Yes but does not form a closed network
Xie, 2013[214]	Argon 514nm ion laser (n=49) Subthreshold micropulse diode laser (n=50)	Xie 2013	6	NE	NE	Yes but does not form a closed network.

AFB = aflibercept ; BVZ=Bevacizumab; PRN or PRN. = pro re nata (as needed); RBZ = ranibizumab; PDT = photodynamic therapy; FAc= Fluocinolone Acetonide implant; mEDTRS= modified ETDRS; FG = focal grid; PRP = pan retinal photocoagulation; TE = treat and extend; PC = photocoagulation; IVTA = intravitreal triamcinolone; DRCRN = Diabetic Retinopathy Clinical Research network; FA = fluorescein angiogram, CRT = central retinal thickness. * main article. [A]= abstract. NE = not extracted.

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APPENDIX A – TABLE 2: EXCLUDED STUDIES (CLINICAL EFFECTIVENESS)

Reference	Reasons for exclusion
O'Day R, Barthelmes D, Zhu M, Wong TY, McAllister I, Arnold J, et al. Predicting retreatment with intravitreal triamcinolone acetonide for diabetic macular edema from baseline characteristics. Paper presented at 43rd Annual Scientific Congress of The Royal Australian and New Zealand College of Ophthalmologists; 19-22 Nov 2011; Canberra: Australia. Clin Experiment Ophthalmo 2011;39:31.	Exclude [abstract with no extractable outcomes]
Nepomuceno AB, Takaki E, Paes De Almeida FP, Peroni R, Cardillo JA, Siqueira RC, et al. A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of diabetic macular oedema. *Am J Ophthalmol* 2013;156(3):502-510.e2.	Exclude [Not relevant study design]
Bressler SB, Qin H, Melia M, Bressler NM, Beck RW, Chan CK, et al. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA Ophthalmology* 2013;131(8):1033-1040.	Exclude [Not relevant outcome]
Ranibizumab and diabetic macular oedema: After laser therapy. *Prescrire Int* 2012;21(125):66.	Exclude [Not relevant study design]
Neubauer AS, Langer J, Liegl R, Haritoglou C, Wolf A, Kozak I, et al. Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser. Clin Ophthalmol 2012;7(1):121-128.	Exclude [Not relevant study design]
Kamura Y, Sato Y, Deguchi Y, Yagi F. Iatrogenic retinal breaks during 20-gauge vitrectomy for proliferative diabetic retinopathy. Clin Ophthalmol 2012;7(1):29-33.	Exclude [Not relevant intervention]
Waqar S, Bullen G, Chant S, Salman R, Vaidya B, Ling R. Cost implications, deprivation and geodemographic segmentation analysis of non-attenders (DNA) in an established diabetic retinopathy screening programme. Diabetes Metab Syndr 2012;6(4):199-202.	Exclude [Not relevant study design]
Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: Evidence from the RESTORE trial. *Br J Ophthalmol* 2012;96(5):688-693.	Exclude [multiple reasons]
Gardner TW. The restore study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Evid Based Ophthalmol 2011;12(4):206-207.	Exclude [Not relevant study design]
Marey HM, Ellakwa AF. Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. Clin Ophthalmol 2011;5(1):1011-1016.	Exclude [multiple reasons]
Kohly RP, Muni RH, Kertes PJ. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Evid Based Ophthalmol 2010;11(4):199-201.	Exclude [Not relevant study design]
Bressler NM, Edwards AR, Beck RW, Flaxel CJ, Glassman AR, Ip MS, et al. Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. *Arch Ophthalmol* 2009;127(12):1566-1571.	Exclude [Not relevant outcome]
Lee HY, Lee SY, Park JS. Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. Korean J Ophthalmol 2009;23(3):153-158.	Exclude [Not relevant study design]
Mohamed S, Leung GM, Chan CKM, Lai TYY, Lee VYW, Liu DTL, et al. Factors associated with variability in response of diabetic macular oedema after intravitreal triamcinolone. Clin Experiment Ophthalmo 2009;37(6):602-608.	Exclude [Not relevant study design]
Gillies MC, Simpson JM, Gaston C, Hunt G, Ali H, Zhu M, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. Ophthalmology 2009;116(11):2182-2187.	Exclude [Not relevant study design]

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Chung EJ, Freeman WR, Azen SP, Lee H, Koh HJ. Comparison of combination posterior sub-tenon triamcinolone and modified grid laser treatment with intravitreal triamcinolone treatment in patients with diffuse diabetic macular oedema. *Yonsei Med J* 2008;49(6):955-964.	Exclude [Not relevant intervention]
Liu LJ, Liu LW, Wang Y. [Effects of laser photocoagulation combined with lecithin-bound iodine and herbal in treating diabetic macular edma]. Int J Ophthalmol 2008;8(4):820-821.	Exclude [Not relevant intervention]
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APPENDIX B FOR QUESTION B6

[PAGES 121 TO 248 OF TABLES DELETED – ACADEMIC IN CONFIDENCE]