National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Aflibercept for treating diabetic macular oedema [ID717]

You are asked to check the ERG report from Aberdeen to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 22 December** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Number of injections assumed by the ERG for aflibercept in year 1 (page 5)

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr>
<td>The ERG has incorrectly interpreted the wording of the SmPC for aflibercept in terms of number of injections specified in the fixed regimen in year 1. There are 12 months in a year. Therefore, 5 consecutive injections followed by an injection every two months would result in a total of 8 injections in the first year, according to the SmPC.</td>
<td>Remove “and the aflibercept dosing in year 1 also appears to be slightly out of line with the SmPC” and similar phrases wherever they appear (e.g. page 101).</td>
<td>Aflibercept SmPC (September 2014): “Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections”

Assuming the schedule below for a patient beginning on aflibercept, by month of the year, there would be no injection in December, as described by the ERG in their report:
<table>
<tr><td>J</td><td>F</td><td>M</td><td>A</td><td>M</td><td>J</td><td>J</td><td>A</td><td>S</td><td>O</td><td>N</td><td>D</td><td>Total</td></tr>
<tr><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td></td><td>8</td></tr>
</table>
</td>
<td>Based upon clinical advice, the ERG have taken the month of the SmPC to relate to four weekly intervals, this enabling a regular dosing schedule. An example of the dosing schedule that could results is as follows:

Thurs 01 Jan 2015 – start of month 1
Thurs 29 Jan 2015 – start of month 2
Thurs 26 Feb 2015 – start of month 3
Thurs 26 Mar 2015 – start of month 4
Thurs 23 Apr 2015 – start of month 5
Thurs 18 Jun 2015 – start of month 7
Thurs 13 Aug 2015 – start of month 9
Thurs 08 Oct 2015 – start of month 11
Thurs 03 Dec 2015 – start of month 13

This gives a total of 9 injections in the first year. But the last injection will straddle the year</td>
</tr>
</table>

			end covering Dec 2015 and Jan 2016 so could argue for only a half injection being costed for the last month of the first year within the model. Note that the ERG revised base case applies 8.50 injections in the first year and [redacted] injections in the second year. It should be borne in mind that the trials also suggested a mean of around [redacted] injections in the first year and [redacted] injections in the second year. As a consequence, if the trial data does include dropouts as seems likely, it may be more reasonable for the ERG revised base case to have applied 9 injections in the first year for those remaining on treatment throughout the first year. No factual error. No revision required.

Issue 2 Number of injections assumed by the ERG for ranibizumab in year 1 (page 5)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG incorrectly state that the company submission assumptions around dosing for ranibizumab are not in line with the trials' data. The estimate for	Remove the wording that states the assumptions for ranibizumab dosing in our submission are not in line with the trials' data on	The model includes the efficacy data from RESTORE, REVEAL, and DRCR.net for ranibizumab. Therefore, an unweighted average of the number of injections reported in these studies was used to inform resource use	The ERG are suggesting that the correct calculation is the weighted average of 8.10 rather than the company unweighted average of 7.93. This is all quite explicit on page 100 of the ERG report.

number of injections in the first year used in the company submission is an average of the numbers cited in the ranibizumab studies included in the network meta-analysis (NMA) – RESTORE, REVEAL, and DRCR.net Protocol I. The ERG are, in fact, suggesting that data on number of injections from one of the trials, DRCR.net. Protocol I, be excluded from our estimate. This would be less in line with the trials' data than in the original submission.	page 5 and similar phrases elsewhere.	estimates for ranibizumab injections in the first year. The SmPC for ranibizumab does not include a fixed dosing regimen to inform the model and therefore the estimate of number of injections must come from other sources. An unweighted average (7.93) was used as it was more conservative than a weighted average (8.1). The average included a median from the DRCR.net Protocol I as mean data was not available. RESTORE and REVEAL reported mean number of injections. Although not ideal, to exclude data on number of injections from a large study included in the NMA and estimates of relative treatment effect would have meant excluding key information. The estimate of resource use would be out of line with the treatment effect estimates from the NMA. The conservative unweighted average would have compensated for the possibility that the mean in DRCR.net may have been lower than the median, which we have no opportunity of knowing.	As the company notes, its unweighted average of 7.93 is based upon the including the median from the DCRC.net trial. The ERG report is also quite explicit on page 100 about the reasons for excluding this median from the calculation for the base case, concluding "*To the ERG this suggests a central estimate of 7.43 ranibizumab injections in the first year, and sensitivity analyses that assume 8.10 and 7.00*". The results of the base case and of the sensitivity analyses are presented in section 5.4 of the ERG report. As a consequence, readers of the ERG report are left in no doubt about the calculations underlying the ERG base case, the reasons for these calculations and the impact of changing the assumptions around these calculations. No factual error. No revision required.

Issue 3 Number of injections assumed by the ERG for aflibercept in year 2 (page 101)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG incorrectly states that the number of aflibercept injections in the VISTA/VIVID studies reported at week 100 may be an underestimate of the number of aflibercept injections	Include a correct reference to the SmPC for aflibercept with regard to the treatment regimen beyond 12 months: *"After the first 12 months of*	VISTA/VIVID included a bi-monthly fixed dosing protocol in year 2 The SmPC for aflibercept does not specify a bi-monthly dosing regimen in year 2. It specifies a treat-and extend-regimen in year 2, meaning less frequent injections for some or all patients	The explanation to the issue raised by the company is that the 100 week point is less than the 104 week point, which is technically the two year point. Consequently, there may be some additional administrations between week 100 and week 104, which are not counted

in year 2. The treatment protocol in VISTA/VIVID (a bi-monthly regimen in year 2) is not the same as the regimen stated in the SmPC which describes a treat-and-extend regimen from 12 months onward. The average number of injections in year 2 is more likely to decrease in clinical practice as an extension of treatment intervals would indicate injections would become less frequent than bi-monthly.	*treatment with [aflibercept], the treatment interval may be extended based on visual and anatomic outcomes."*	depending on visual and anatomic outcomes. The model does not include comparative efficacy data for aflibercept and ranibizumab in year 2. An indirect comparison was not possible beyond 12 months due to the different trial designs. Therefore, maintenance has been assumed in both treatment arms in the model. Therefore, any difference in injection frequency is not balanced with a consideration of the impact on comparative efficacy.	within the trial average number of injections at the 100 week point. No factual error. No revision required.

Issue 4 Number of monitoring visits assumed by the ERG for ranibizumab in year 1 (page 6)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG states that the revised ranibizumab SmPC has a monitoring schedule more in line with that of aflibercept. This is incorrect, particularly with reference to the first year. The SmPC for aflibercept describes a proactive fixed dosing regimen in the first year with no requirement for monitoring in between. The dosing regimen in the first year	Remove "'in line with that of aflibercept" on page 6 and "suggests something similar for ranibizumab" on page 103.	The SmPC for aflibercept specifies a different regimen compared with that of ranibizumab in the first year. One is a proactive fixed dosing regimen which is unaffected by monitoring (except in terms of discontinuation rules) whilst the other is reactive, with frequency being determined by monitoring. Moreover, the ranibizumab studies included in the NMA and economic model for treatment effect in the first year (RESTORE, REVEAL, DRCR.net Protocol I) studied reactive ranibizumab regimens. The efficacy and number of	The revised ranibizumab SmPC has a monitoring schedule that is more in line with that of aflibercept when compared with the original ranibizumab SmPC monitoring schedule. This is because the original ranibizumab SmPC monitoring schedule specified monthly monitoring during the first year. The ERG report is explicit about this on pages 102 and 103, providing the relevant quotes from the relevant SmPCs. The paragraph following the quotes from the ranibizumab SmPCs also provides the ERG interpretation of the SmPCs on this

is not determined by monitoring. This was also the case in the pivotal VISTA/VIVID studies. The SmPC for ranibizumab is a more reactive dosing regimen that is determined by visual acuity, anatomical parameters and/or disease activity, established at the monitoring visits. Until September 2014, the SmPC for ranibizumab stated monthly monitoring of visual acuity. The revised SmPC allows the physician to determine frequency. Therefore, this may still be as frequent as monthly, if deemed as required. The studies that were included in the NMA and the model (RESTORE, REVEAL, DRCR.net Protocol I) used monthly monitoring to establish treatment frequency.		ranibizumab injections in these trials was based on a monthly monitoring regimen, at least in the first year included in the NMA. It is uncertain how less frequent monitoring would affect these outcomes. Treatment frequency was not determined by monitoring in the first year of VIVID and VISTA as it was protocol driven. The ranibizumab SmPC says: "*Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed…Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters…If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened*	point and in the opinion of the ERG is reasonably balanced. No factual error. No revision required.

		accordingly." The ERG has made predictions about what will happen over the short and medium term without any supporting evidence or justification. According to NICE methods of technology appraisal, the comparator is defined as routine rather than future practice in the NHS. Similar assumptions about monitoring should be applied in year 2 if trial data is used to inform treatment frequency. As in year 1, monitoring did not inform the treatment regimen in VIVID or VISTA in year 2, but did in the included ranibizumab studies.	

Issue 5 Presentation of all-cause mortality data (page 46)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG suggests that incorrect data have been presented with regard to information on deaths in VISTA and VIVID. The data provided are correct but represent different analyses. The ERG indicates that the difference between the number of deaths in the aflibercept and laser groups warrants consideration. This is incorrect as there was no significant	Remove phrase "the ERG were not in the position to confirm which source was correct", Remove 'warrants consideration', Add and define "all-cause mortality" to the title and text or clarify the reasons for /category of deaths cited here.	The current wording is a misleading presentation of the data regarding deaths in VIVID and VISTA provided in the submission. Figure 5 and 6 show patient flow and 'reasons for discontinuation' and are not part of the safety analysis, as presented in Section 6.9. The NMA includes data from the initial presentation of VISTA/VIVID data by Schmidt-Erfurth at Euretina in 2013, as these were available at the time of the first systematic review. This included an additional death in the 2Q8 arm that occurred in year 2 but was	There was inconsistency in the number of deaths reported in different parts of the company submission and this was clearly highlighted on pages 46 and 47 of the ERG report. The 'correct' numbers could not be confirmed and therefore the sentence "*the ERG were not in the position to confirm which source was correct"* was included in the report. The ERG agree there was not a significant difference in the number of

difference between the groups in terms of number of deaths and in other parts of the ERG report no significant difference has been described as 'no difference'. Moreover, the reason for / category of death (i.e. all-cause mortality) is not correctly specified here, which may be misleading to anyone who has not read the full submission.		included in the year 1 database and later excluded from 52 week analyses. The other safety data presented for weeks 0 to 52 are all in line with Korobelnik that showed no difference between arms in terms of vascular deaths (2 in each of the three arms) and cites two additional non-vascular deaths in the 2Q8 arm due to B-cell lymphoma and lung neoplasm. This was included in the clarification response along with details on the 100 week data of which [redacted] of the 26 total deaths [redacted] judged to be drug-related, as described in the submission. All relevant study publication references were provided to the ERG.	deaths between treatment arms (as explicitly stated in the ERG report). However, the ERG regarded the numerical difference - even though not statistically significant - as clinically relevant. The ERG refer to deaths assuming all-cause mortality and, although not explicitly stated, this could be implied by the lack of a specific cause attached to death. No factual error. No revision required.

Issue 6 References to all-cause mortality in VISTA and VIVID and the REVEAL data (page 66)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG have conducted a new indirect comparison but there is insufficient data provided to be able to assess factual accuracy. References to the REVEAL study data are incorrect/unclear (Korobelnik is cited).	Removal of 'clinical study report' Correct references to REVEAL data Provide event data used.	Limited information from the REVEAL study is available from a published abstract by Ohji, et al. 2012 and on clinicaltrials.gov. The REVEAL abstract cites a fatal car accident but provides little other data on safety. It is unclear whether all information has been reported. No further data are presented in the study results on clinicaltrials.gov.	The source data for the REVEAL study, which the ERG obtained, came from the clinical study report. This indicated 0/128 deaths in the laser arm and 1/133 in the ranibizumab arm. The ERG appreciate that these data could have been provided in their report, but consider this as a minor omission not as a factual inaccuracy. The source of this data was Ohji 2012 (correctly referenced) or (CSR), but not

		Moreover, in addition to the lack of detailed information from REVEAL, the ERG questions the relevance of REVEAL data in other sections of the report (page 67) due to its primarily Asian population.	Korolbenik, this was an error in referencing on behalf of the ERG. However, since ref 40 was appropriate, no change has been made.

Issue 7 Reference to total (all-cause) deaths in VISTA and VIVID

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 1, the report refers to 5 deaths in the aflibercept arm and 0 deaths in the laser arm. This is incorrect. There were 2 deaths in the laser arm in the first 52 weeks. 1 death in the aflibercept arm occurred in year 2 and was excluded in the final 52 weeks analysis. No reference is made to where these data are obtained, at which time point, which arm of the study, and the category of death referred to.	The ERG report should cite 12 month data as published the peer-reviewed publication of the VISTA/VIVID data (Korobelnik, et al. 2014) which showed no differences between groups in terms of vascular deaths (2 events in each arm), and 2 other non-vascular deaths in the 2Q8 arm due to B-cell lymphoma and lung neoplasm.	Data from a peer-reviewed publication should be used which provides a balanced and more detailed assessment of the deaths in VISTA and VIVID. The response to the clarification letter refers to 5 events for aflibercept and 2 for laser in terms of all-cause mortality. The clarification response also describes the 1 patient who died in year 2 was included in the year 1 database and in early conference presentations that were available at the time of the first systematic review. However, this patient was excluded at a later date from the 52 week study analysis and the Korobelnik publication. All study references were provided with the submission.	Page 46 of the ERG report details the information provided for mortality and highlight the discrepancies that exist within the company submission, which does not directly match that of the peer-reviewed publication by Korobelnik et al. 2014. For the aflibercept 2Q8 versus laser, Figures 5/6 (for VISTA and VIVID) indicate 4 deaths in 2Q8 and 1 in laser, while Figure 56 indicates 5 in 2Q8 and 2 in laser. The ERG agree that the number of reported deaths on page 2 of the Summary section (5 deaths in the aflibercept group and 0 in the laser group) is not correct. This was a typographical error rather than a factual inaccuracy and it should have been 5 and 2 deaths for the aflibercept group and the laser group respectively, as per Figure 56.

			Typographical error amended.

Issue 8 Unlicensed status of bevacizumab (page 13, 15)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The report incorrectly refers to use of bevacizumab as 'off-label". Bevacizumab is formulated for use in oncology. Therefore the reformulated intravitreal product is unlicensed.	Replace off-label with unlicensed	In line with general definitions.	We accept the company's point. Bevacizumab is licensed for use in oncology. It is worth noting, however, that bevacizumab has not been included as a comparator in the company submission and this minor slip does not impact whatsoever on the results and conclusions of this appraisal. No revision required.

Issue 9 Definition of differences

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 56 and elsewhere, there is an inconsistent use of the words 'difference' and 'different'	Include appropriate definitions of differences or state the numerical value of the difference, with p-value.	In some parts of the report, numerical differences are defined as 'no difference' and in others these differences 'warrant consideration'. This appears subjective. It is appropriate to define differences as numerical, statistically significant, and/or clinically significant in the context where the	The comment seems to refer to a matter of written English style and preferences. Page 56 does not pose any problem in terms of appropriateness and transparency of information. No factual error. No revision required.

		actual values are not stated alongside p values.	

Issue 10 Discontinuation (page 7 and 108)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG refers to the impact of discontinuation on mean number of doses reported in the trials. However, the number of doses assumed for aflibercept in the company submission in year 1 is based on the fixed dose regimen specified in the SmPC and on a physician survey in years 2-5, assuming the same for aflibercept and ranibizumab in the absence of comparative efficacy data.	Specify which assumptions would be affected (i.e. assumptions based on clinical studies).	Addition of clarity to identify which costs would be underestimated.	This is related to issue 1, and as discussed above due to discontinuations being within the model it could have been more appropriate to have assumed 9 aflibercept doses in year 1. No factual error. No revision required.

Issue 11 Subgroup data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
It is indicated that the “company has access” to subgroup data for central retinal thickness from VISTA and VIVID.	Amend to “there is data available”	The current wording suggests that the company has not provided relevant subgroup data. All requested data has been provided.	It is correct that data by subgroup were supplied to the ERG during the clarification process. However, it is also perfectly correct to state that the company has access to these data.

The ERG has access to the subgroup data. All data requested in the clarification letter was provided.			No factual error. No revision required.

Issue 12 Fellow eye involvement (page 117 and 115)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG indicate that "it seems reasonable to apply a common [redacted] fellow eye involvement at baseline". This is an inaccurate measure of anticipated fellow eye involvement (FEI). Moreover, it is also unclear if and how that has been included in the revised basecase.	Clarify the calculation of fellow eye involvement and if and how this has been included in the revised base case.	This figure contrasts greatly from the 35% (taken from RESTORE) that was accepted in the appraisal of ranibizumab for DMO (TA274) where it was referred to in terms of expected practice (Section 3.29 and 3.46 of the Final Appraisal Document). This suggests that the figure is more a description of the study and analysis than the actual rate of FEI. As discussed in the ERG report, a proportion of patients included in the VISTA and VIVID studies had already had anti-VEGF treatment. This differs from the RESTORE study used as the primary source in TA274. As described at clarification stage, data on FEI at baseline was not collected as part of the VISTA/VIVID study. The data provided was captured as part of medical history. Therefore, the data may not be appropriate for estimating FEI as FEI was not defined or categorised. Moreover, as described in the clarification response, this data provides no detail on category or severity of FEI. A much smaller	The [redacted] estimate is based upon the data supplied by the company at clarification and as presented in tables 65 and 66 of the ERG report [redacted] with FEI and [redacted] without). Table 69 of the ERG report, titled *Pooled bilateral distribution and percentage FEI at baseline*, is also very explicit about the calculation of [redacted] this being immediately prior to the company quotation of the ERG report. Tables 76, 77, 78, 79 and 80 of the ERG report also undertake a sensitivity analysis setting FEI involvement at baseline to 46% indicating that the ERG base case has used something other than 46%. The ERG acknowledge that this estimate is somewhat higher than has been applied in previous assessments, but it does not represent a factual error as such. Whether this was applied within the ERG base case is not explicit within section 5.4. However, the quote by the company from

		proportion were actually treated for DMO in the fellow eye during the study. This data was collected as part of the safety analysis. The SmPC states that 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 in the first 52 weeks. However, even this data is limited and may overestimate those treated for DMO and those with clinically significant DMO in the fellow eye at baseline (not 52 weeks). For consistency between appraisals, it would be appropriate to use the figure from TA274. However, we conservatively opted for something that better represents clinical practice in the UK (46% from the physician survey) and was between study estimates.	elsewhere within the ERG report does suggest that this estimate was used, or at least was very likely to be used, by the ERG. A footnote as to the method could have been included within section 5.4 of the ERG report referring to changing cell I13 of the *PH* worksheet to be equal to [redacted] but it should perhaps be borne in mind that this is an explicit "up-front" input to the model, which requires minimal specification to identify. The ERG corrected company model results are relatively insensitive to this variable. Table 76 of the ERG report outlines that revising the rate to 46% changes the ICER versus laser from £33,921 per QALY to £33,657 per QALY. Tables 77, 78, 79 and 80 undertake similar sensitivity analyses for the comparison with ranibizumab and again show relative insensitivity to this variable. No factual error. No revision required.

Issue 13 Consistency with TA274

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG indicates that a laser visit of £131 is consistent with TA274. It is unclear from the information provided how this is	Clarify the wording regarding consistency with previous appraisals.	In TA274 (Section 3.15 and 3.41 of the final guidance), it states that an injection visit was costed the same as a laser visit (£150) and that that bottom-up costing calculated to support this	Pages 121 and 122 of the ERG report discuss this in some detail, the relevant quote being "*It seems more reasonable to apply the £131 to retain some consistency*

the case.		was reasonable. The cost of an injection visit in the submission for aflibercept for DMO is in line with that proposed by the ERG in TA305 (not TA283, as described in the report) aflibercept for CRVO (£194). To be consistent with previous appraisals (TA274), the cost of a laser visit would be the same as an injection visit, as proposed in TA283. It is unclear whether ERG expert opinion is a fair representation of routine practice in England and Wales and whether financial flows are the same in devolved administrations.	*with the TA274 ranibizumab for DMO*". The ERG report notes the £150 per laser administration within TA274, also noting that this was based upon BZ23Z outpatient procedure. The then current reference costs were £150 for BZ23Z and £184 for BZ22Z. It also notes that the 2012-13 reference costs give a cost of £117 for the BZ23Z outpatient procedure (n=801,444) and £131 for the more involved BZ22B (n=78,836). To cost a laser administration it might have been more consistent with TA274 to have applied the current BZ23Z £117 cost. Still, the £131 for BZ23Z used in the ERG base case is little different from this. Applying the £117 BZ23Z outpatient cost would have marginally worsened the cost effectiveness of aflibercept against laser. The company is correct to note that Novartis assumed the same administration cost for ranibizumab as for laser. Applying the £193 aflibercept administration cost to laser administrations (cell C24 of the *Cost_Input* worksheet) improves the ICER from £33,921 per QALY to £33,123 per QALY. No revision required.

Issue 14 Factual accuracy of exploratory and sensitivity analyses undertaken by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
It is not possible to check the factual accuracy of the revised modelling in the time provided as this required reprogramming of the submitted model using the text provided in the ERG report.			No comment needed.

Issue 15 DRCR.net (Protocol T) as an ongoing study (page 142)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG states that this study is ongoing. Initial topline study conclusions have been put into the public domain.	Add that information from this study is expected to be presented prior to the Appraisal Committee meeting in January 2015.	At previous points in the appraisal process, NICE have asked Bayer to provide information on this study, although it is not a Bayer study. Topline data is conclusions are available here: http://newsroom.regeneron.com/releasedetail.cfm?releaseid=876732, however more data will not be available until the DRCR network study group presents/publishes its findings. Although the study does not include the licensed dose of ranibizumab in the UK, comparative efficacy of the different doses has been assessed in the RISE and RIDE studies (Nguyen et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012 Apr;119(4):789-801.)	According to the information available at ClinicalTrials.gov the study is ongoing. The primary outcome of the study has been assessed at 1 year. The 1-year results are available but have not been published yet. Nevertheless, some secondary outcomes are assessed at 2 years (see ClinicalTrials.gov), which categorises the study as ongoing. No factual error. No revision required.