Bayer response to ACD for aflibercept DMO – Data Appendix

Q1. HAS ALL OF THE RELEVANT EVIDENCE BEEN TAKEN INTO ACCOUNT?

The results of the submitted network meta-analysis that showed a significant difference between aflibercept and ranibizumab in terms of mean change in BCVA from baseline have recently been confirmed by the publication of the results of the DRCR.net Protocol T study[1]. This head-to-head randomised controlled trial reported a mean change in visual acuity from baseline to 1 year of +13.3 letters with aflibercept and +11.2 letters with ranibizumab (P=0.03 for aflibercept versus ranibizumab). The higher number of letters gained with aflibercept compared with ranibizumab was also reflected in the subgroup of patients with a baseline CRT of 400 micrometres and greater (+16.2 and +12.4 letters respectively).

Further information about the results of this study are available in the attached publication. Only data directly relating to our comment in response on the ACD to Q1 has been reported here.

Q2. ARE THE PROVISIONAL RECOMMENDATIONS SOUND AND A SUITABLE BASIS FOR GUIDANCE TO THE NHS?

Issue 1 and 2: Inappropriate resource use inputs and assumptions

The ERG estimated 8.55 and 5.45 injections in the 1st and 2nd year for aflibercept. This is not in line with the Summary of Product Characteristics (SmPC) for aflibercept and is an overestimate of the number of injections in years 1 and 2.

In response to the ERG report, we conducted an online survey of 10 UK ophthalmologists (screening criteria and questions attached in Appendix A). Clinicians estimated an average of 6.5 injections for aflibercept in year 1 and 4.1 aflibercept injections in year 2, which is lower than that estimated in the VIVID and VISTA studies and supports the above hypothesis that a similar number of injections should be assumed for aflibercept and ranibizumab in years 1 and 2.

Table 1: Number of injections per year with aflibercept

Respondent	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
1	6	3	3	0	0	0
2	6	3	1	1	0	0
3	7	3	0	0	0	0
4	8	6	4	4	4	3
5	8	5	0	0	0	0
6	5	3	3	0	0	0
7	8	4	2	0	0	0
8	3	2	2	1	1	0
9	7	6	4	3	3	3
10	7	6	4	0	0	0
Average	**6.5**	**4.1**	**2.3**	**0.9**	**0.8**	**0.6**

[1]The Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. N Engl J Med. 2015 Feb 18. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1414264 [cited 12 March 2015)

Table 2: Monitoring visits per year with aflibercept

Respondent	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
1	4	3	3	3	3	0
2	3	2	2	2	1	1
3	5	7	3	3	3	3
4	10	6	4	4	4	3
5	4	3	0	0	0	0
6	10	6	6	0	0	0
7	8	6	5	3	0	0
8	3	2	2	2	1	0
9	5	5	4	4	4	0
10	4	2	1	0	0	0
Average	**5.6**	**4.2**	**3.0**	**2.1**	**1.6**	**0.7**

Table 3: Shared monitoring/administration visits

Respondent	Q7
1	0
2	0
3	0
4	80
5	100
6	0
7	100
8	50
9	30
10	80
	44.0

Moreover, the recently published results of DRCR.net Protocol T (referenced previously in Q1) also confirmed fewer injections were required with aflibercept compared with ranibizumab, although the posology differed somewhat to that defined in the UK marketing authorisation.

Issue 3: Inappropriate estimate of the unit cost of laser administration visits

The ERG estimated a lower cost for a laser visit compared with an injection visit based on the opion of one clinician that a laser visit takes less time than an injection visit. To test the estimate in the ERG base case more robustly, we conducted an online survey of 34 ophthalmologists (screening criteria and questions listed in Appendix C, results in Appendix D). The average time spent by a healthcare professional (HCP) with a patient in relation to a visit to perform laser was 23.7 minutes. The average time spent by a HCP with a patient in relation to a visit to perform an anti-VEGF injection was 22.30 minutes. This suggests a difference of 24 seconds. The ophthalmologist administered laser in 100% of cases. Given that there is uncertainty over laser as a relevant comparator for DMO, this survey was conducted with physicians treating branch retinal vein occlusion who use laser. Moreover, laser visits would not be costed by indication.

Moreover, in independent economic evaluations such as Prescott, et al. (2014)[2] laser is grouped alongside intravitreal injections using the code BZ23Z in the NHS reference costs.

Issue 4: Inappropriate estimate of fellow eye involvement using VIVID and VISTA data

Several epidemiology publications for DMO in the UK highlight that the number of people with clinically significant DMO is much lower than those with any form of DMO[3,4,5.]

Issue 6: Availability of shift tables from VIVID and VISTA

Shift tables may be employed within the original submitted economic model by selecting 'Yes' from the 'Shift Tables' tab on the 'Exectutive Summary' worksheet.

PROPOSED AMENDED ERG BASE CASE FOR AFLIBERCEPT VERSUS LASER

Based on the discussion around the evidence above, we propose the following revised ERG base case using data already submitted in our original model, submission and response to clarifications. This is a more robust and justified base case for aflibercept:

- Resource use inputs in year 1 based on clinical studies including the number of ranibizumab injection from RESTORE, REVEAL and DRCR.net Protocol I in year 1 (7.93 injections) and monthly monitoring visits for laser as described above.
- Resource use inputs in year 2 based on the assumption of equivalence (no indirect comparison available) including 4 injections of aflibercept and ranibizumab in year 2.
- Identical cost for laser and injection visit (includes OCT monitoring) (£196)
- Fellow eye involvement based on clinical practice (46%)
- Inclusion of individual patient data (shift tables) from VISTA/VIVID in year 1
- Mortality rate from Preis et al.

The ERG provided their version of our submitted model in response to a request made by us during the ACD consultation. Below are the assumptions used in the ERG base case versus laser (ICER £33,921) compared with the assumptions that we have used in our proposed revised ICER versus laser (£21,718). The ERG version of the model has an additional worksheet named "ERG". This worksheet has various possible selections to include or not to include their revisions or use our original inputs and assumptions.

Table 4 – Description of ERG base case

Model inputs	Description by ERG	ERG Base Case	Revised - ERG changes employed

[2] Prescott G, et al. Improving the cost-effectiveness of photographic screening for diabetic macular oedema: a prospective, multi-centre, UK study. Br J Ophthalmol. 2014 Aug;98(8):1042-9. HTA report available at: http://www.journalslibrary.nihr.ac.uk/hta/volume-17/issue-51#abstract (cited 12th March 2015)

[3] Minassian, et al. Prevalence of diabetic macular oedema and related health and social care resource use in England. Br J Ophthalmol 2012;96:345e349. doi:10.1136/bjo.2011.204040,

[4]Keenan TDL, et al. United Kingdom National Ophthalmology Database Study: Diabetic Retinopathy; Report 1: prevalence of centre-involving diabetic macular oedema and other grades of maculopathy and retinopathy in hospital eye services, Eye (2013) 27, 1397–1404

[5] Scanlon PH, et al. Epidemiological Issues in Diabetic Retinopathy. Middle East Afr J Ophthalmol. 2013 Oct-Dec; 20(4): 293–300.

Correct discounting	ERG_discounting	Yes	Yes
Revise cost of blindness	ERG_blind_cost	Yes	Yes
Make cost of blindness monthly	ERG_blind_cost_mthly	Yes	Yes
Discount costs of blindness	ERG_blind_cost_disc	Yes	Yes
Utility regression	ERG_Util_Regress	GEE	GEE
Utility equal step for each health state	ERG_Util_Equal_Step	Yes	Yes
Mortality from DMO	ERG_DMO_Mort	Yes	No
DMO rate of 10 letter increase	ERG_DMO_increase	Yes	Yes
DMO rate of worsening	ERG_DMO_dec_val	1.00%	1.00%
Correct 2nd eye tx calculations	ERG_FEI_correct_tx	Yes	Yes
Condition FE treatments by those alive	ERG_FEI_Tx_cond_alive	Yes	Yes
FE baseline DMO from VISTA/VIVID	ERG_FEI_DMO_Baseline	Yes	No
ERG QoL WSE proportion BSE	ERG_FEI_WSE_QoL_Prop	Yes	Yes
ERG laser admin costs	ERG_laser_cost	Yes	No
ERG ranibizumab injections	ERG_RANI_inj	Yes	No
ERG aflibercept injections	ERG_AFLI_inj	Yes	No
ERG AE costs	ERG_AE_costs	Yes	Yes
ERG Rani PAS	ERG_RANI_PAS	0%	0%
ERG rounding for utilities	ERG_Util_Round_DP	2	2
Tx_Input worksheet – Injections - Aflibercept – reverted to 8.55 in year 1 in line with clinical trials – AS PER ERG BASE CASE		**Yes**	**Yes**
Tx_Input worksheet – Monitoring - Laser – set to 12 monitoring visits in year 1 in line with clinical trials (approach taken by ERG)		**No**	**Yes**
"Executive summary" worksheet – shift tables employed?		**No**	**Yes**
Resulting ICER		**£33,921**	**£21,718**

The ICER for aflibercept versus laser in the ERG base case was £33,921. With these more balanced inputs, **the revised ERG base case ICER for aflibercept versus laser is £21, 718**. Including the number of aflibercept injections stated in the SmPC reduces the ICER further to £20,858.

INCORPORATING WATCH AND WAIT AS THE APPROPRIATE COMPARATOR FOR PATIENTS WITH CRT AT BASELINE OF <400 MICROMETRES

Early studies refer to observation or deferred laser versus laser. A recently published systematic review[6] cites the Early Treatment Diabetic Retinopathy (ETDRS) study and the Diabetic Retinopathy Study (DRS), cited in. However, the watch and wait regimen specifically refers to patients being watched whilst their CRT is under 400 micrometres and being treated with ranibizumab, when their CRT passes the 400 micrometres level determined in NICE guidance TA274.

Appendix A - DMO physician online survey

Introduction – Ethical undertaking

Questionnaire background

This questionnaire relates to patients with diabetic macular Oedema (DMO). DMO is an ocular complication of type 1 and type 2 diabetes. Diabetes may cause capillaries in the eye to become abnormally permeable and leak fluid into the retinal tissue of the macula, causing DMO. The effect of DMO is vision loss and, if left untreated, can lead to blindness.

Clinically significant DMO (CSDMO) has been defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group as occurring when there is thickening of the retina involving the centre of the retina (macula) or the area within 500 µm of it, if there are hard exudates at or within 500 µm of the centre of the retina with thickening of the adjacent retina, or if there is a zone of retinal thickening one disc area or larger in size, any part of which is within one disc diameter of the centre of the retina.

We would like you to keep this clinically significant DMO patient population in mind when responding to questions throughout this questionnaire.

You will be asked to consider hypothetical scenarios. We would appreciate receiving answers for an "average DMO patient" as we are interested in the way you would treat a DMO patient in general, irrespective of baseline characteristics, e.g. ischaemic status, baseline visual acuity, age etc or patients at each end of the spectrum of the disease.
We understand that for some questions it may be necessary to provide approximations based upon your professional experience.

To ensure consistent interpretation, please read the definitions below.

Treatment visits are appointments with an ophthalmologist where aflibercept would be administered to eye(s) affected by DMO.

Monitoring visits are appointments with an ophthalmologist where eye(s) affected by DMO are assessed, but no treatment is planned. It is assumed that a monitoring visit includes an eye exam (visual acuity) and OCT test (or, where applicable, fundus photography).

Structure of the questionnaire

The questionnaire you are about to enter starts with screening questions, to confirm your eligibility to participate in this study. This is followed by a section covering your clinical experience and current practice. Throughout the questionnaire we ask that you keep in mind your professional experience in treating patients with clinically significant DMO.

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[6] Evans JR, Michelessi M, Virgili G. Laser photocoagulation for proliferative diabetic retinopathy. Cochrane Reviews Library, November 2014. Available at http://www.cochrane.org/CD011234/EYES_laser-photocoagulation-for-proliferative-diabetic-retinopathy (cited 12th March 2015)

The questionnaire then asks questions related to resource use, both in the treatment and monitoring of patients with clinically significant DMO.

We would like you to consider typical patient experiences and metrics throughout this questionnaire. You might like to think of these patients as the “average” or “typical” patients. We understand that for some questions it may be necessary to provide approximations based upon your professional experience.

List of Abbreviations

Abbreviation	Definition
CSDMO	Clinically Significant Diabetic Macular Oedema
DMO	Diabetic Macular Oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluourescein Angiography
OCT	Optical Coherence Tomography

Screening questions:

S1 Please indicate specialty.

Ophthalmology	( ) **continue**
Other	( ) **end**

S2 Do you currently treat patients for Diabetic Macular Oedema (DMO)? Note: “treat” is deemed to represent the decision to administer laser or drug therapy and long-term follow-up of patients [*Definition of DMO: an ocular complication of type 1 and type 2 diabetes. Diabetes may cause capillaries in the eye to become abnormally permeable and leak fluid into the retinal tissue of the macula, causing DMO. The effect of DMO is vision loss and, if left untreated, may lead to blindness]*

Yes	( ) **continue**
No	( ) **end**

S3 What percentage of your time is spent managing patients, as opposed to teaching, research, or administrative functions?

≥50%	( ) **continue**
<50%	( ) **end**

S4 How many patients with DMO do you usually see in a given month? (This can include newly diagnosed patients and patients with ongoing treatment or monitoring post treatment.)

≥10	( ) **continue**
<10	( ) **end**

Respondent background *(not part of screening criteria)*:

Q1 For how many years have you been practising ophthalmology?

(open numeric, years)

Q1a Please specify your specialty within ophthalmology, if applicable
(Open text)

Q2 Currently in which healthcare setting(s) do you predominantly (>50% of your patients) manage patients with DMO?

Public (NHS) setting	( )
Private setting	( )
Other (please specify)	( )

Q3 How many DMO cases do you personally manage per year? Please consider newly diagnosed patients and patients ongoing treatment or monitoring post-treatment.
(open numeric, whole numbers only)

Resource use:

DMO treatment

Q4 Please indicate in the table below the expected average number of aflibercept treatments administered per eye per year, based on the patients with DM.

Note: number of treatments refers to one injection of aflibercept

	Average number of treatments administered, **per affected eye**					
Therapy chosen	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+ (annual)
A. Aflibercept	Q4A1	Q4A2	Q4A3	Q4A4	Q4A5	Q4A6

DMO monitoring

Q5 Please indicate in the table below the expected frequency of aflibercept monitoring visits per eye, per patient. Please write “0” if no visits are conducted.

Therapy chosen	Average number of monitoring visits **per eye**, per patient					
	1.Year 1	2.Year 2	3.Year 3	4.Year 4	5.Year 5	6.Year 6+ (annual)
A. Aflibercept	Q5A1	Q5A2	Q5A3	Q5A4	Q5A5	Q5A6

Q6 In which proportion of patients on the aflibercept therapy would you expect to perform both treatment and monitoring at the same time, rather than in separate visits.

Therapy chosen	Shared monitoring visit
A.Aflibercept	(numeric, 0-100%)

Appendix B

BRVO physician survey (Source of response to duration of laser question)

Screening questions:

S1 Please indicate specialty.

Speciality	
Ophthalmology	( ) **continue**
Other	( ) **end**

S2 Do you currently treat patients for Branch Retinal Vein Occlusion (BRVO)? Note: “treat” is deemed to represent the decision to administer laser or drug therapy and long-term follow-up of patients

Treatment of patients with BRVO	
I currently treat patients for BRVO	( ) **continue**
I do not currently treat patients for BRVO	( ) **end**

S3 How many patients with BRVO do you usually see in a given month? (This can include newly diagnosed patients and patients with ongoing treatment or monitoring post treatment.)

Patients with BRVO I usually see in a month	
≥15 patients with BRVO each month	( ) **continue**
<15 patients with BRVO each month	( ) **end**

Questions

Which type of laser is commonly used in your practice?
(Free text)

How much time on average does a HCP spend with a patient in relation to a visit to perform laser. Please consider minutes as time unit
(numeric)

How much time on average does a HCP spend with a patient in relation to a vist to perform an anti-VEGF injection? Please consider minutes as time unit
(numeric)

Survey results

Laser type used	Duration of laser visit (mins)	Duration of injection visit (mins)
Argon	30	15
Argon	25	17
Argon	30	10
Argon	15	8
Yellow	30	30
Argon	30	60
Pascal Argon	30	30
Argon	20	15
Pascal	7	10
Pascal	30	30
Argon	25	15
Argon	40	60
Argon	15	15
Pascal	20	20
Argon	45	30
Argon	5	10
Argon green laser	20	15
532nm double frequency YAG laser	5	10
Pascal	20	20
Pascal	15	25
Pascal	30	60
Argon	20	15
Pascal	45	45
Pascal	30	30
Grid laser	20	15
Diode	10	10
Macular laser sector retinal laser	60	45
Yellow	5	15
Argon	20	20
Krypton	10	10
Argon	30	20
Pascal	20	20
Argon	30	5
Argon	30	20
Pascal	30	15
Sub threshold diode laser	15	15
Macular grid, Diode laser	15	20
AVERAGE (MINS)	**23.70**	**22.30**