Single Technology Appraisal – Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer

PART 2 – RESPONSE TO NON-PRIORITY ERG CLARIFICATION QUESTIONS

B15 Could you please clarify the following points regarding the economic analysis

- **Section 7.2.9. Please provide 95% confidence intervals for the mean dose values in Table 29 p133 and mean number of cycles per month observed in Table 33 p137. In addition, please provide for each of the six treatment groups separately.**

Tabulated below are the mean dose and cycle durations with confidence intervals as requested.

The cycle durations for the bevacizumab arms are based on the mean bevacizumab cycle durations and the cycle duration for all the other arms are based on the oxaliplatin cycle duration. Cycle duration was similar when using oxaliplatin doses as when using bevacizumab for the bevacizumab containing arms. (see footnote to table 2 below).

The confidence intervals for the cycle durations were calculated based on a sample size (n) of the total number of cycles. This assumes independence between cycles, which may under estimate confidence intervals.

In the economic model the mean per cycle dose was calculated by dividing the mean dose by the mean number of cycles. The updated table below shows the mean dose per each cycle calculated directly from the patient level data, which was calculated as part of the exercise for calculating the confidence intervals for the dose. Hence there is a slight variance between the mean values presented here and the mean values used in the economic model. The only variances however greater than 1% between the figures used in the model and those presented in the table below are for capecitabine and oxaliplatin. We can confirm that updating the model with the mean values presented below does not materially affect the results of the economic analysis; the ICER for B-XELOX vs XELOX+-P increases by only £24 and B-FOLFOX-6 vs FOLFOX-6+-P increases by only £46.

Table 1: Mean dose (mg) per cycle observed in NO16966 study by arm (ITT)

Arm	Data	5-FU BOLUS	5-FU INFUSION	LEUCOVORIN	OXALIPLATIN	BEVACIZUMAB	CAPECITABINE
FOLFOX +A	Mean	1,333	2,035	683	139	360	
	Lower CI 95%	1,307	1,998	668	136	352	
	Upper CI 95%	1,359	2,072	697	142	369	
FOLFOX +-P	Mean	1,347	2,056	696	140	163	
	Lower CI 95%	1,331	2,034	687	138	41	
	Upper CI 95%	1,363	2,078	704	142	286	
FOLFOX + P	Mean	1,339	2,047	682	137	163	
	Lower CI 95%	1,316	2,015	669	134	41	
	Upper CI 95%	1,362	2,078	695	139	286	
FOLFOX	Mean	1,355	2,067	710	144		
	Lower CI 95%	1,333	2,036	699	141		
	Upper CI 95%	1,378	2,098	721	146		
XELOX +A	Mean				215	549	42,949
	Lower CI 95%				210	537	41,862
	Upper CI 95%				219	561	44,035
XELOX +- P	Mean				218	214	44,521
	Lower CI 95%				215	10	43,741
	Upper CI 95%				221	418	45,301
XELOX + P	Mean				217	214	44,388
	Lower CI 95%				213	10	43,312
	Upper CI 95%				221	418	45,464
XELOX	Mean				219		44,666
	Lower CI 95%				215		43,531
	Upper CI 95%				223		45,800

*the confidence intervals are based on a sample size (n) of the number of patients

Table 2: Mean number of cycles per month observed in NO16966

	FOLFOX	FOLFOX+P	FOLFOX+B[T]	XELOX	XELOX+P	XELOX+B[T]
Per Protocol (days)	14	14	14	21	21	21
Actual Cycle duration (days)	16.65	16.78	16.23	23.13	23.45	23.13
CI	16.47 / 16.82	16.62 / 16.94	16.09 / 16.38	22.92 / 23.33	23.25 / 23.64	22.86 / 23.21
	5-FU-based regimens			**Capecitabine-based regimens**		
Average cycle duration (days)	16.55 16.46 / 16.65			23.21 23.09 / 23.32		
Cycles per month used in model	**1.84**			**1.31**		

[T]*Mean B-XELOX and B-FOLFOX cycle duration is 23.17 (CI 22.99 ; 23.35) and 16.32 (CI 16.17 ; 16.46) when based on oxaliplatin doses*

B16 Could you please clarify the following information in the appendices

- **Appendix E1. As the model submitted by the manufacturer is a cohort model the mean costs of treatment are appropriate. Please clarify whether the costs have been sampled using the quartiles described in table 51 on p182 and in table 52 rather than the standard error of the mean, which would be incorrect.**

- **Appendix E3. The manufacturer's submission states that a Beta Pert distribution was used to estimate uncertainty in adverse event costs. It is unclear whether the quartiles listed in Table 51 or the 50% and 150% of the mean were used as the low and high estimates. Please describe how the parameters for the beta pert distributions were calculated. Please also describe any assumptions made, including how the mode was estimated.**

- **Appendix E3. For the PSA a Beta (utility*1000, (1-utility)*1000) distribution was used to model the uncertainty in the utility values. Please use a Beta distribution that fits to the confidence intervals of the utility data.**
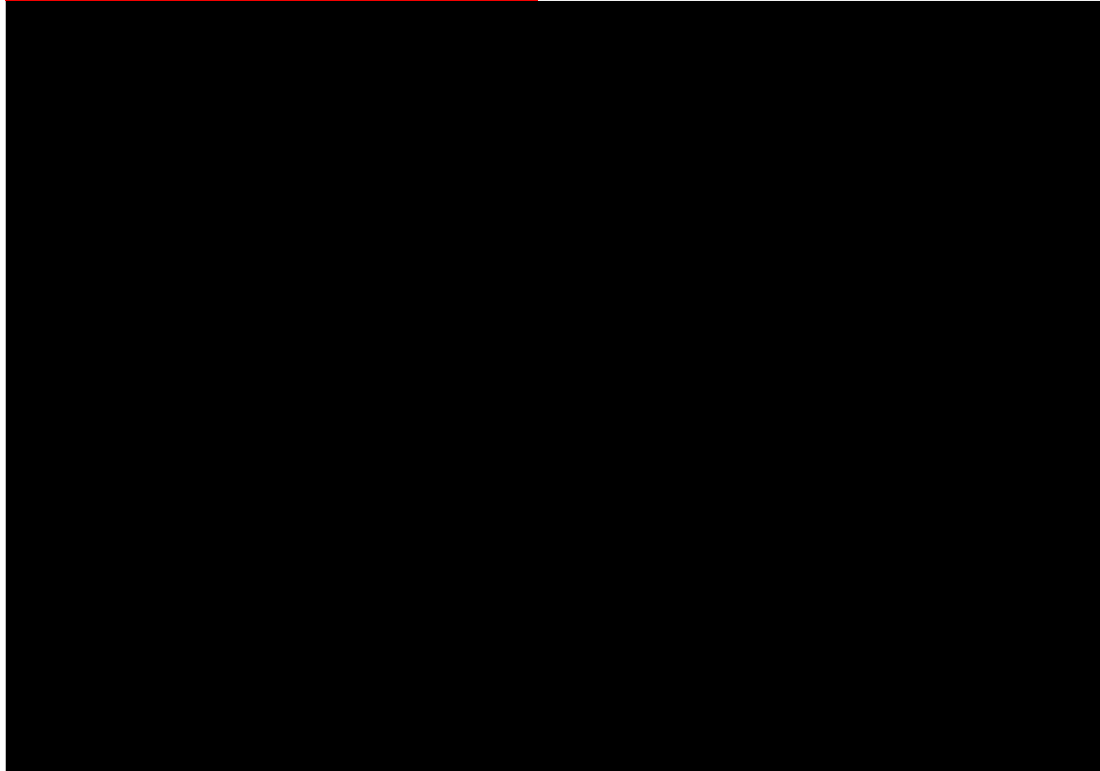
The model assumes a minimum and maximum value of 50% and 150% of the mean respectively for all adverse event costs and monthly progression free and does not use the inter-quartile range.

The model has been amended with a beta distribution that fits the confidence intervals of the utility data as requested. For the PFS_T health state the s.e. was 0.02 it was assumed that this was the same standard error for the PFS_{PT} health state. The standard error of the mean utility for the progressive disease health state has not been reported in the literature however the standard errors at each individual time point that the utility was measured in the source trial is available. The standard error of the estimated average utility at each time point is in the range of 0.02 – 0.03 or less. Given that there seems to be a small variability in average utility at each time point

one can assume that the standard error of the overall mean utility would be less than the standard error of the individual means at each time point. A standard error or 0.03 has been assumed in the PSA.
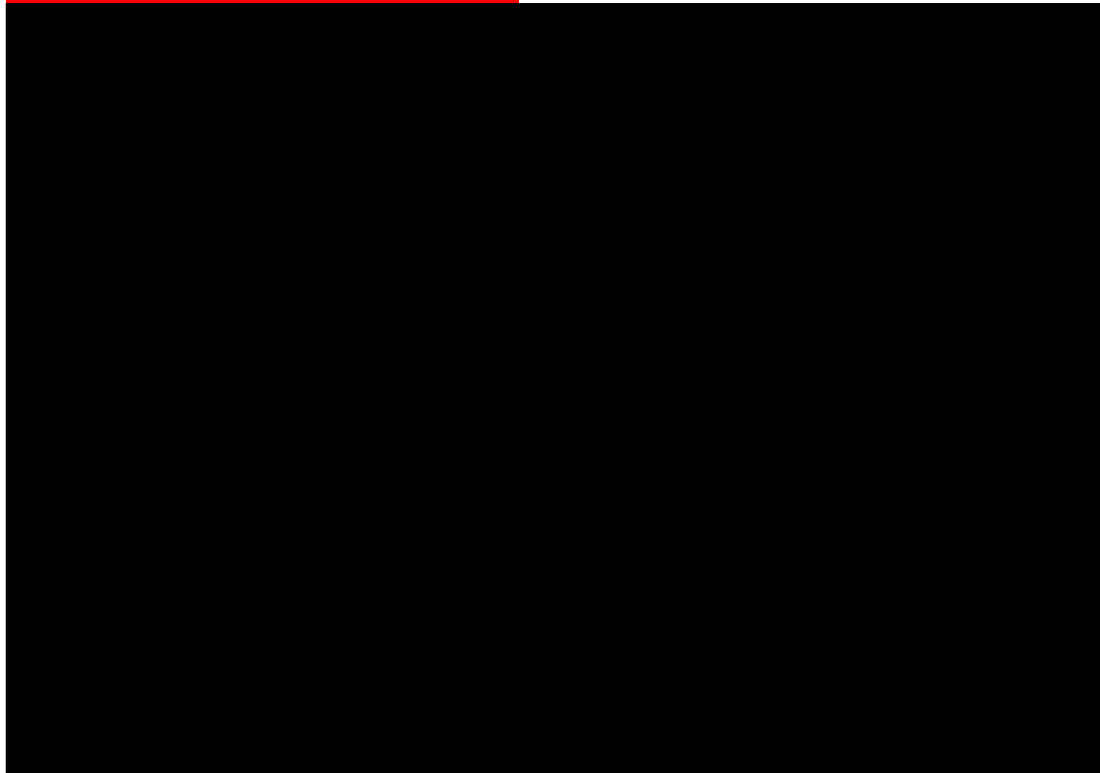
Below are the results of the PSA based on the pooled analysis using all 6 arms of the NO16966 as per scenario 1 presented in appendix A of part 1 of our response to the clarification questions and utilizing the standard error to fit the distribution around the utility values as per the above request.

Scatter Plot: B-XELOX vs XELOX+-P

Mean = £36,205

Scatter Plot: B-FOLFOX-6 vs FOLFOX-6

Mean = £36,907

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Chart: Probability of Being Cost-Effective (y-axis, 0 to 1) versus WTP (x-axis, 0 to 100000). Legend: B-FOLFOX-4, B-FOLFOX-6, B-XELOX, XELOX, FOLFOX-6, FOLFOX-4, FOLFIRI mdg, FOLFIRI dg.