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BY E-MAIL

Dear Phil,

SINGLE TECHNOLOGY APPRAISAL –
Bevacizumab in combination with oxaliplatin and either 5-fluorouracil or capecitabine for the treatment of metastatic colorectal cancer

Thank you for providing us with the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal.

This response to the ACD relates specifically to improving the certainty and precision of the estimated ICERs in response to the criticisms within the ACD of the current base case.

Roche also intends to submit some revisions to the associated Patient Access Scheme which accompanies this appraisal in order to provide improved alignment with this revised base case. However, before we make this further submission we need to conclude some further discussions with the Department of Health. We will submit the revised details of the scheme as soon as possible being mindful of the date of the next Appraisal Committee meeting on 27th January 2010.

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Summary

The ACD states: "*The Committee concluded that the cost-effectiveness estimates of bevacizumab as a first-line treatment of metastatic colorectal cancer (£36,400 and £31,500 per QALY gained) were at the lowest end of a range and plausible adjustments to the key model inputs would increase these ICERs substantially. The ICERs were therefore associated with a great deal of uncertainty."* The areas of concern highlighted by the Committee can be summarized as follows:

1. The NHS resource costs of operating APAS and the subsequent impact on the ICERs.

2. The operation of the APAS in the context of an intermittent treatment strategy

3. Bevacizumab treatment duration in clinical practice compared with that observed in the NO16966 study

4. The incremental pharmacy and administration cost associated with adding bevacizumab to XELOX or FOLFOX

5. The health state utility values used in the economic model

In order to fully address each of these points Roche has conducted further detailed research and analysis (described in detail in section 1 below). This has resulted in revised base case ICERs for bevacizumab being presented which account for the criticisms listed within the ACD.

Revisions to base case ICERS

Revised parameter	Marginal effect on ICERs of each revision	
	B-XELOX	B-FOLFOX
Utility Values	+£647	+£560
APAS Operating costs	+£164	+£113
Preparation and Pharmacy	- £678	- £1014
Cumulative impact	+£133	- £314

Upon further investigation of points 1 and 5 it was found that, as suggested by the Committee, the base case ICERs increased.

With regards to point 4, we have conducted a direct time and motion observation study, which demonstrated that preparation and administration of bevacizumab actually incurred less cost than we originally estimated, thus reducing the ICERs.

Based on the further research conducted to investigate point 2 and 3, no amendment to the economic modelling was considered necessary. Clarifications and discussion are provided in section 1 below regarding these points.

The cumulative effect of each of the revisions to the model parameters (ie to APAS operating costs, utility values, pharmacy and drug administration costs) resulted in ICERs (£36,494 B-XELOX ; £31,122 B-FOLFOX) very similar to the original base case presented in the ACD.

We hope that the findings of this additional research will serve to validate the robustness of the current ICERs and allay the concerns of the committee.

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

1) The NHS resource cost of operating APAS and the subsequent effect on the ICER

In section 4.14 of the ACD states: "*The Committee agreed that the impact of the scheme in practice was uncertain and that incorporating higher administration costs would increase the ICER estimates*"

Following this feedback, Roche conducted extensive research with pharmacists, NHS business managers, and NHS finance and operations experts to identify the activities required to set up and administer the APAS and estimate the employee time required to conduct these activities. Full details of this research is supplied in appendix A.

An activity based costing approach was taken to calculate a mean per patient cost of operating the APAS.

The activities identified were split into 4 categories:

1. Initial set-up activities
2. Ongoing monthly activities
3. Per patient activities
4. Per treatment cycle activities

The total estimated employee time is summarised in table 1 below, categorised by the frequency with which the activity would occur (see appendix A for more details)

Table 1: Estimated Activity Time Per Instance of Activity (see breakdown in appendix A)

Activity Frequency	Person Minutes (hours)
Initial Set-up activities (once per trust)	1470 (24.5)
Ongoing monthly activities (each month)	90 (1.5)
Per patient activities (one-off per patient) *	25 (0.4)
Per treatment cycle (each cycle) [T]	5 (0.08)

*Includes an assumed 15 minutes time to investigate queries

[T] Experts indicated this may be less if these activities were batched and performed per month

The time required to complete each activity was allocated to a per patient time (shown in table 3) based on a three year time frame and the parameter estimates listed in table 2.

The throughput of patients on the APAS per trust was calculated based upon the number of patients expected to be treated with bevacizumab between years one to three as calculated in the Budget Impact section of our original submission (section 8). The number of patients treated with bevacizumab is expected to be 2,186, 3,279, and 4,313 in years one, two and three respectively.

Table 2: Estimated APAS Activity Years 1-3

Parameter	Estimate	Source
Average prevalence of patients on APAS in England and Wales	1,870	Incidence over years 1-3 * average duration of Bevacizumab treatment in NO16966
The average number of trusts adopting APAS	124	Number of trusts currently estimated to be using Oxaliplatin, IMS, 2009
Cumulative patients per trust	79	9778/124
Average Prevalence per trust	15	1870/124

Table 3: Resource consumption per patient by frequency of activity

Activity Frequency	Person Minutes per patient*	Source
Initial Set-up Activities	20	Total per trust / cumulative patients per trust over years 1-3
Ongoing Monthly Activities	41	Total per month / average prevalence of patients in a trust * the average number of months a patient remains on APAS
Per Patient Activities (One-off per patient)	25	Total as per estimated in Appendix A
Every Cycle	45 XELOX 66 FOLFOX	Per cycle cost * number of bevacizumab treatment cycles estimated by economic model
Total	131 XELOX 152 FOLFOX	

* The difference between FOLFOX and XELOX arises due to the difference in cycle duration (every 2 and every 3 weeks respectively) between the regimens.

The estimated time per patient of administering the APAS was 131 minutes and 152 minutes per patient for XELOX and FOLFOX based regimens respectively.

The unit cost per minute for each of the professionals conducting the activities was calculated based on the mid-point salaries taken from the 2009 Agenda for Change pay scales combined with the overhead and salary on-costs taken from the PSSRU (PSSRU, 2008). Since overhead estimates for all the professionals involved were not available, overheads for these professional were assumed be the same as for a hospital pharmacist. As per assumed in the PSSRU, the calculation of unit costs per hour were based on 1565 working hours in a year. The resulting unit costs are shown in the table below.

Table 4: Unit costs applied in the calculation of the operating costs of APAS

	Band 4	Band 6	Band 8a
Salary (2009 mid-points)	19,495	28,816	42,434
Salary on-costs (assumed 21%)	4,094	6,051	8,911
Overheads	7,743	7,743	7,743
Total	31,332	42,610	59,088
Per working hour (assumes 1565 per annum)	**20**	**27**	**38**

Based on the above, the cost per patient of operating the APAS over years 1 to 3 is estimated to be £57 and £67 for B-XELOX and B-FOLFOX respectively. (calculations provided in appendix C)

Using these revised estimates in the economic model increases the ICER's for B-XELOX and B-FOLFOX by £164 and £113 respectively.

2) The operation of the APAS in the context of an intermittent treatment strategy

The ACD states in section 4.14: *"The Committee understood that intermittent treatment is commonly used in UK clinical practice and chemotherapy treatment is often restarted if there are signs of disease progression. The Committee understood that in these circumstances (that is with any signs of disease progression) the patient access scheme would no longer apply."*

Post the publication of the ACD Roche held a clinical expert advisory board with 6 leading UK oncologist specialising in the treatment of mCRC (Roche ACD ad-board, London 2009). The advisory board provided explicit input as to the nature of current treatment of mCRC in the UK. There was general agreement that intermittent treatment is used by some clinicians within the UK.

Roche can now confirm the APAS scheme will still be applicable and available should clinicians choose to use intermittent treatment of oxaliplatin-based chemotherapy plus bevacizumab. The APAS would be applicable regardless of treatment breaks so long as patients are restarted on oxaliplatin-based treatment.

For the avoidance of doubt, the 12 month cap will relate to 12 cumulative months of treatment and not 12 calendar months, therefore treatment breaks will be accounted for within the APAS should patients be treated intermittently.

If a patient is transferred to an alternative chemotherapy regimen this would signify the start of second line therapy and thus they would no longer qualify for the APAS, as bevacizumab will not be recommended for second line therapy. This definition was suggested by the experts attending the advisory board with respect to intermittent treatment for patients in the UK.

3) Bevacizumab treatment duration in clinical practice and its effect on the ICERs

The ACD suggests that in clinical practice bevacizumab may not be as cost effective as estimated based on the NO16966 study due to longer treatment duration of bevacizumab in UK clinical practice compared to the trial. The ACD states that the committee considered that *"the extra bevacizumab costs"…* associated with a longer treatment duration… *"would outweigh any additional survival benefits of bevacizumab, given its modest impact on progression-free and overall survival.*"

Firstly, it is important to note that such a conclusion can not be drawn with any degree of certainty in the absence of the clinical data required for testing this hypothesis. Additionally it is unclear whether or not the committee considered the effect of the price cap on the cost of increasing treatment duration.

Secondly, we will present evidence below that suggests that in clinical practice treatment duration of bevacizumab is likely to be similar to or less than that observed and modeled on the NO16966 study.

Clinical Advisory Board

Following publication of the ACD, Roche facilitated an advisory board (Roche ACD ad-board, London 2009) to obtain the views from clinical experts on issues highlighted by the Committee. On the subject of treatment duration the main points of feedback from the experts were as follows:

a) As recognised by the committee, intermittent treatment, such as that specified in the COIN study (Adams, 2009), is becoming more prevalent within UK clinical practice. This typically leads to a shorter treatment duration compared to the NO16966 study.

b) It was considered that should bevacizumab be given positive NICE guidance it is likely to be added to the treatment strategy that is currently being employed, either intermittent treatment or continuous.

c) Irrespective of whether a continuous or intermittent strategy was used bevacizumab would only likely be given in combination with chemotherapy. It would also be expected that it treatment with oxaliplatin was stopped due to either a planned break or unacceptable toxicity then treatment with bevacizumab would also typically be stopped at this time.

The feedback from the advisory board therefore suggests that treatment duration with bevacizumab in clinical practice would be similar to that of oxaliplatin, and the average duration of treatment is likely to be less that that observed in the NO16966 study due to a proportion of patients being treated with intermittent treatment strategies.

Real world evidence of bevacizumab treatment duration

Reassurance on the duration of continuous bevacizumab and chemotherapy (median 6 month in NO16966) treatment in clinical practice can be given based on the BRiTE and ARIES observational studies conducted in the USA.

BRiTE (Kozloff et al 2009) is described fully in Section 6.8 of our original submission. This was a permissive programme recruiting patients requiring first-line chemotherapy for metastatic colorectal cancer (mCRC), other entry requirements were minimal, as was data collection, so that population would be expected to be fairly representative of a routine clinical cohort.

Clinicians could use any first-line combination of chemotherapy plus bevacizumab. In practice 96% of the 1,953 patients recruited received a dose of 5mg/kg bevacizumab every 2 weeks (in accord with the NO16966 protocol and what Roche is seeking NICE endorsement for) and more than 60% of patients received a fluoropyrimidine plus oxaliplatin combination as their cytotoxic regimen. As shown in Table 5. the median bevacizumab treatment duration in BRiTE was shorter than in NO16966, but the median PFS and OS were actually longer indicating that any truncation of treatment was not at the expense of efficacy.

ARIES was a prospective observational study. It was designed to investigate safety and efficacy in patients who would not necessarily satisfy the stringent entry criteria for conventional clinical trials. Patients from 244 sites were eligible if they had mCRC and received bevacizumab as part of their 1st or 2nd line treatment. This was the sole entry criterion. Between November 2006 and September 2008, 2041 patients with unresectable colorectal cancer were recruited (1538 first-line and 503 second-line). There was no protocol specified regimen, dose or duration stipulated, and no exclusions based on clinical characteristics. Data was collected via an electronic CRF at baseline and then quarterly from then on. Whilst only treatment duration of bevacizumab was captured in the BRiTE study treatment duration of both oxaliplatin and bevacizumab were recorded in ARIES. As presented in table 5, treatment durations of oxaliplatin and bevacizumab in patients that received 1st line B-FOLFOX (ARIES reports little use of B-XELOX) are consistent with the BRiTE study and less than that of the NO16966 study. Also as observed in the NO16966 study, the treatment durations of bevacizumab and oxaliplatin are very similar. PFS and OS was similar to that seen in BRiTE and exceed those reported in the NO16966 study.

Table 5: Bevacizumab treatment duration and key clinical outcomes in patients receiving chemotherapy in the NO16966 study and BRiTE study

	NO16966 study N=701*	**BRiTE study N=1,953**	**ARIES study N=969**
Median duration of first-line bevacizumab (months)	6.0	5.4	4.86
Median duration of first-line oxaliplatin (months)	5.9	NA	5.06
Median PFS (months)	9.4	9.9	10.3
Median OS (months)	21.3	22.9	24.8

* Patients from the 2 x 2 part of the study only i.e. only those randomised to bevacizumab or placebo.

4) The incremental pharmacy and administration cost associated with adding bevacizumab to XELOX or FOLFOX

The ACD states: "*The Committee further noted that the administration costs of B−FOLFOX and B-XELOX were assumed to be very similar to the administration costs of FOLFOX and XELOX. The Committee considered that the addition of a bevacizumab infusion to either XELOX or FOLFOX would incur greater additional administration costs than those assumed by the manufacturer*."

The economic model assumes that the incremental pharmacy and administration cost, per cycle, of adding bevacizumab to either XELOX or FOLFOX is £42.

Roche notes, in TA176 the addition of cetuximab to FOLFOX or FOLFIRI was assumed to incur zero incremental pharmacy or drug administration costs. However given the concerns expressed by the committee Roche commissioned a time and motion study, following publication of the ACD, to gain a more precise estimate of the incremental resources consumed in preparing and administering bevacizumab.

Three preparation episodes and three administration episodes of bevacizumab infusions were observed by an independent research group (pH Associates) at the Mount Alvernia Hospital in Guildford. The type of activity, start stop times, and the job title and grade of the healthcare professional performing the tasks were recorded. A summary of the results is provided in table 6 below (the full set of results is provided in Appendix B).

Table 6: Healthcare professional time required to prepare and administer bevacizumab

	Pharmacy Preparation (mins)	Nurse Administration (mins)
Mean	**19.4**	**15.4**
Median	19.4	14.2
Min	17.6	13.9
Max	21.3	18.1
St Dev	1.9	2.3

The estimated cost of hospital nurse and pharmacy time (accounting for overheads, qualifications, and salary on costs) taken from the PSSRU (PSSRU, 2008) and inflated to 2009 costs are provided below.

Table 7: Unit costs taken from the PSSRU (PSSRU, 2008) and inflated to 2009 costs

Healthcare Professional	Per hour	Per patient contact hour [T]	Per patient contact hour inflated to 2009
Hospital Pharmacist (band 6)	£32	£45	£46
Pharmacy Technician	Not available	Not available	Not available
Nurse Team Manager (band 7)	£33	£74	£63*
Nurse Team Leader (band 6)	£29	£65	
Nurse (band 5)	£23	£43	

** Average across bands*; [T] *calculated as total annual cost divided by estimated hours of patient contact for nurses and patient related activity time for pharmacists*

To estimate the cost of each infusion, the inflated PSSRU unit costs (see table 7 above) for patient contact time (nurses), or patient related activity time (pharmacists), were applied to the results of the time and motion study. It was assumed that nurses of band 5 through 7 would administer bevacizumab and so the average cost per hour across these bands was used (£63). In the absence of the cost per hour of a pharmacy technician it was assumed that a hospital pharmacist would perform all preparation activities. This will there overestimate the true cost of preparation as the results of the time and motion study indicate that preparation time is split between the pharmacist and the technician.

Table 8: Estimated bevacizumab preparation and administration cost per dose

Activity	Cost per cycle
Preparation	£15
Administration	£16
Total (preparation and administration)	£31

Conclusion

Whilst it was speculated by the committee that the preparation and administration of bevacizumab per cycle would cost more than that currently applied in the economic model (£42), the empirical evidence from this time and motion suggests the reverse.

Amending the economic model to reflect the results of the time and motion study reduces the ICERs by £677 and £1,012 when adding bevacizumab to XELOX and FOLFOX-6 respectively.

5) The health state utility values used in the economic model

It is noted in the ACD that the utility values used within the economic model appeared to be high.

There are 3 health state utility values used within the Roche economic model:

1. Progression free survival (PFS) whilst patients are on treatment – 0.77
2. PFS post cessation of chemotherapy – 0.79
3. Post 1st line progression – 0.68

It is important to note that the ICERs are not sensitive to changes to the utility value used for the post progression health state. Reducing this parameter value from 0.68 to 0.60 alters the ICERs by less than £20, hence the validity of this assumption is not considered further within this response.

The Guide to Methods for Technology Appraisals clearly states the most robust estimates of utility value would "*be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults."*

Ideally such EQ-5D results would come directly from the trial upon which the economic model is based. Quality of life data was not captured in NO16966 and thus the model uses the next most appropriate source, which is the EQ-5D results from a recent phase III study in 1st line mCRC in which patients received either FOLFIRI or cetuximab in combination with FOLFIRI.

The subsequent figure of 0.77 is consistent with that accepted for use for PFS in both the previous NICE appraisal of bevacizumab, in the 1st line treatment of mCRC (TA 118, 2005) where a value of 0.80 was used for PFS in the analysis conducted by ScHARR, and recently in the appraisal of cetuximab (TA 176, 2009) where 0.77 is used for PFS.

It is therefore reasonable to consider that the value of 0.77 is a robust estimate of the utility of patients in 1st line PFS with mCRC and is consistent with the NICE Guide to Methods. However in recognition of the concerns of the committee the new base case assumes that 0.77 applies throughout PFS i.e. the increase in utility for PFS patients off treatment has been removed and 0.77 represents the average utility value for PFS on and off treatment.

Reducing the PFS off treatment utility value to 0.77 increased the ICERs by £647 and £560 for B-XELOX and B-FOLFOX respectively.

2 WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE

In section 4.14 the ACD states: "*Nevertheless, the Committee understood from the ERG that the ICERS for both B-XELOX and B-FOLFOX increased if bevacizumab treatment continued beyond that of oxaliplatin.*" It appears that this conclusion was drawn based on the results of the sensitivity analysis conducted by the ERG (section 3.25, ACD). As discussed in section 1 above, the evidence does not allow for such a conclusion to be drawn given that this scenario has not been tested and therefore the benefit associated with an increase in treatment duration are unknown. Additionally it is not clear as to whether the committee considered the impact of the price cap on the cost of increasing treatment duration.

3 WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS

Several issues have been raised within the ACD that were assumed to increase the ICER, although alternative ICERs accounting individually or cumulatively were not reported. Roche has therefore attempted to address the concerns raised within the ACD and we have presented further cost effectiveness analysis, which we would like to request that the Committee consider at its next meeting, alongside the revised proposals for an accompanying patient access scheme.

The patient access scheme that has been approved for NICE appraisal by DH has been designed to address all of the issues raised during the consultation on the scheme. Roche believes that the flexibility and logistical options available within the scheme will mean that it will be utilised effectively by NHS Trusts. The scheme is applicable both in the NHS setting and also for those NHS Trusts which require it in the homecare setting. Homecare provides a greater level of cost effectiveness to the NHS resulting in reduced ICERs compared to the hospital setting due to reductions in drug administration costs.

4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

No comments.

We hope this feedback is useful to support the further deliberations of the Committee.

Yours sincerely,

Appendix A: Operating cost of APAS

Appendix B: Full Time and Motion Results

Appendix C: APAS administration cost calculations

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