BEVACIZUMAB IN COMBINATION WITH FLUOROPYRIMIDINE-BASED CHEMOTHERAPY FOR THE FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER – A SINGLE TECHNOLOGY APPRAISAL

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List of abbreviations

APAS	Avastin Patient Access Scheme
CCTR	Cochrane Controlled Trials Register
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CIC	Commercial-In-Confidence
CRC	Colorectal cancer
CVAD	Central Venous Access Device
EQ-5D	EuroQol-5D
ERG	Evidence Review Group
HRQoL	Health-Related Quality of Life
FOLFIRI	intravenous 5- fluorouracil plus folinic acid plus irinotecan
FOLFOX	intravenous 5- fluorouracil plus folinic acid plus oxaliplatin
5-FU	5-fluorouracil
HUI	Health Utility Index
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention-To-Treat
mg/d	milligrams per day
mg/kg	Milligram per kilogram
MLE	Maximum Likelihood Estimate
MS	Manufacturer's Submission
NICE	National Institute for Health and Clinical Excellence
PD	Progressive disease
PFS_{PT}	Progression free survival post treatment
PFS_{T}	Progression free survival on treatment
PSA	Probabilistic Sensitivity Analyses
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
RECIST	Solid evaluation criteria in solid tumours
RR	Relative Risk
SEM	Standard Error of mean
STA	Single Technology Appraisal
VEGF	vascular endothelial growth factor
XELIRI	oral capecitabine plus intravenous irinotecan

XELOX	oral capecitabine plus intravenous oxaliplatin

1. SUMMARY

1.1 Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by NICE, and is appropriate to the NHS. Although the majority of the MS reflects the use of bevacizumab in combination with oxaliplatin-based chemotherapy as first line therapy (for patients not previously treated for metastatic disease) in individuals with histologically confirmed metastatic colorectal cancer, it does not reflect the broader population outlined in the licensed indication and final scope issued by NICE. The licensed indication permits the use of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer but does not specify a line of treatment. Whilst the NICE scope broadly reflects the licensed indication; the manufacturer is seeking approval for first line use only. The MS defines the intervention as bevacizumab in combination with oxaliplatin and either 5-fluoruracil or capecitabine for people with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable. The MS considered oxaliplatin-including chemotherapy regimens without bevacizumab as the most relevant comparator, as reflected in the scope. However, a comparison with irinotecan-including chemotherapy regimens without bevacizumab was considered of limited clinical and economic relevance because it is not commonly used within the UK. While the systematic review undertaken in the MS did not consider irinotecan-based chemotherapy regimens as a relevant comparator, the manufacturer undertook an economic evaluation with irinotecan-based chemotherapy (given the small number of patients for whom this comparison is relevant) for completeness (using data from a published, peer reviewed, mixed treatment comparison). The outcome measures identified in the scope were all relevant and included overall survival, progression free survival, response rate, adverse effects and health related quality of life (HRQoL). The results provided are presented in terms of cost per quality adjusted life year (QALY) with a time horizon of eight years, which is equivalent to a life time horizon in the population of interest, with the perspective of costs taken from a NHS and Personal Social Services perspective.

1.2 Summary of submitted clinical effectiveness evidence

- The manufacturer's submission to NICE includes a systematic review of the clinical effectiveness literature. Although two randomised controlled trials were identified, one as first line therapy (the NO16966 trial) and one in second-line therapy (for previously treated patients with metastatic disease, E3200 trial), the manufacturer is seeking approval for first line use only (and therefore the N016966 trial forms the main pivotal evidence in the submission). The manufacturer claims that they could not demonstrate a cost-effectiveness case for the use of bevacizumab in second-line therapy.

- The NO16966 trial was a phase III, multicentre, multinational, two-arm, randomised, open label study with the primary objective of confirming the non-inferiority of XELOX (oxaliplatin plus capecitabine) compared with FOLFOX-4 (oxaliplatin plus 5-fluorouracil and folinic acid) in adult patients with histologically confirmed metastatic colorectal cancer who had not previously been treated. Following randomisation of 634 patients, the open label study was amended to include a 2x2 factorial randomised (partially blinded for bevacizumab) phase III trial (n=1401) with the co-primary objective of demonstrating superiority of bevacizumab in combination with chemotherapy (B-XELOX or B-FOLFOX-4) compared with placebo (P-XELOX or P-FOLFOX-4). The dose of bevacizumab was 5 mg/kg every two weeks (B-FOLFOX-4) or 7.5 mg/kg every three weeks (B-XELOX).

- The manufacturers' primary pooled analysis of superiority (using the intention to treat population) in the NO16966 trial showed that after a median follow up of 28 months, the addition of bevacizumab to chemotherapy (B-XELOX / B-FOLFOX-4 combined) significantly improved progression free survival and overall survival compared with chemotherapy alone (P-XELOX/ P-FOLFOX-4/ XELOX/ FOLFOX-4 combined) in adult patients with histologically confirmed metastatic colorectal cancer not previously treated (median progression free survival: 9.4 versus 7.7 months [absolute difference, 1.7 months]; hazard ratio, 0.79; 97.5% CI: 0.72 to 0.87; p=0.0001; median overall survival: 21.2 versus 18.9 months [absolute difference, 2.3 months]; hazard ratio, 0.83; 97.5% CI: 0.74 to 0.93; p=0.0019).

- A secondary pooled analysis of superiority, restricted to patients in the second 2x2 factorial part of the NO16966 study (as per the original statistical trial plan [B-XELOX / B-FOLFOX-4 combined versus P-XELOX/ P-FOLFOX-4 combined] and which the ERG believe to be more appropriate) found similar results (median progression free survival: 9.4 versus 8.0 months [absolute difference, 1.4 months]; hazard ratio, 0.83; 97.5% CI: 0.72 to 0.95; p=0.0023; median overall survival: 21.3 versus 19.9 months [absolute difference, 1.4 months]; hazard ratio, 0.89; 97.5% CI: 0.76 to 1.03; p=0.0769).

- The manufacturers' pooled analysis of non-inferiority (using the eligible patient population and the intention to treat population) showed that the XELOX (XELOX/P-XELOX/B-XELOX combined) and FOLFOX-4 (FOLFOX-4/ P-FOLFOX-4/ B-FOLFOX-4 combined) based regimens were equivalent for both progression free survival (p=not significant, values not reported) and overall survival (p=not significant, values not reported). No analysis was undertaken for the factorial design (P-XELOX/B-XELOX combined versus P-FOLFOX-4/B-FOLFOX-4 combined).

- A pre-defined subgroup analysis on progression free survival found that the statistical superiority of bevacizumab plus chemotherapy was evident in the XELOX subgroups (B-XELOX versus P-XELOX; hazard ratio, 0.80; 97.5% CI: 0.66 to 0.96; p=not reported) but did not reach the significance level in the FOLFOX-4 subgroups (B-FOLFOX-4 versus P-FOLFOX-4; hazard ratio, 0.89; 97.5% CI: 0.74 to 1.06; p=not reported). Additional post hoc exploratory analyses (following the results from the Adjuvant Colon Cancer End Points [ACCENT] study, which found that there was a significant and direct correlation between time to recurrence after surgery and survival after recurrence in patients whose disease recurred after surgery and adjuvant treatment) showed that removing the subgroup of patients that may have slower tumour progression after adjuvant treatment (an imbalance between treatment groups with regard to an important prognostic factor which was not recognised at the start of the NO16966 trial), significantly improved (i.e. lowered) the hazard ratios for adding bevacizumab to chemotherapy compared with chemotherapy alone for both overall survival and progression free survival. Depending on the analyses conducted (e.g. exclusion of patients with prior adjuvant chemotherapy from all four treatment arms of the factorial study, or from FOLFOX groups only or from P-FOLFOX group only) the hazard ratios for overall survival ranged from 0.83 to 0.85 ($p<0.03$) and the hazard ratios for progression free survival ranged from 0.74 to 0.77 ($p<0.0001$). Although this may be plausible, the ERG note that caution should be exercised as this is a post hoc exploratory analysis.

- The majority of adverse events were generally associated with cytotoxic chemotherapy. FOLFOX-4 based regimens were generally associated with increased neutropenia/ granulocytopenia and XELOX based regimens were generally associated with increased diarrhoea and hand and foot syndrome. Adverse events that could be potentially related to bevacizumab included increased frequencies of high blood pressure, proteinuria, bleeding, gastrointestinal perforation, thromboembolic events and wound healing complications. Serious (grade 3) or life threatening (grade 4) adverse events that occurred more commonly in patients receiving bevacizumab plus chemotherapy (B-XELOX / B-FOLFOX-4 combined) than those receiving chemotherapy alone (P-XELOX/ P-FOLFOX-4/ XELOX/ FOLFOX-4 combined) were thromboembolic events (7.8% versus 5.1%), hypertension (4.0% versus 0.8%), proteinuria (3.5% versus 0.9%) and bleeding problems (1.9% versus 1.5%), respectively. Grade 3 and 4 gastrointestinal perforations and wound healing complications were all rare (<1%). Similar results were observed when that data were restricted to the factorial analyses.

- The majority of the treatment discontinuations were attributable to chemotherapy related events rather than related to bevacizumab. Adverse events that could be potentially related to bevacizumab accounted for treatment discontinuation in 5.2% of patients in the bevacizumab plus chemotherapy group (B-XELOX / B-FOLFOX-4 combined) compared with 2.4% in the chemotherapy only (P-XELOX/ P-FOLFOX-4 combined) group (no data reported for the comparison against P-XELOX/ P-FOLFOX-4/ XELOX/ FOLFOX-4 combined). The statistical analysis comparing the rates of discontinuation between treatment groups were not reported in the MS or in the manufacturer's supplementary evidence.

1.3 Summary of submitted cost effectiveness evidence

The submitted cost effectiveness evidence reports on QALYs using the data from the N016966 trial. The ERG requested several changes to the modelling (including additional analyses) and a summary of the resulting incremental cost effectiveness ratios (ICER) is presented below.

Scenario	**ICERs (£ per QALY saved)** B-XELOX vs. XELOX	B-FOLFOX6 vs FOLFOX6
MS original analysis		
Without APAS : Analysis using data from all 6 arms of N016966, XELOX and FOLFOX arms pooled	£ 82,098	£ 94,989
With APAS : Analysis using data from all 6 arms of N016966, XELOX and FOLFOX arms pooled	£ 34,170	£ 41,388
MS supplementary data (all with APAS)		
Analysis using data from all 6 arms of N016966, XELOX and FOLFOX arms pooled	£ 35,912	£ 36,569
Analysis using the 2x2 part of N016966, XELOX and FOLFOX arms pooled	£ 48,111	£ 39,771
Analysis using 2x2 part of N016966, XELOX and FOLFOX arms unpooled	£ 35,662	£ 62,714
Analysis using the 2x2 part of N016966, XELOX and FOLFOX arms pooled, without prior adjuvant treatment	£ 36,006	£ 31,174

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

- The manufacturer conducted a limited but systematic search for clinical and cost-effectiveness studies of bevacizumab and its use in colorectal cancer. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include more free text terms or to include other databases.

- The NO16966 trial is of reasonable methodological quality (with some limitations), and measured a range of outcomes that are as appropriate and clinically relevant as possible.

1.4.2 Weaknesses

- The processes undertaken by the manufacturer for identifying and screening references for inclusion in the systematic review are inappropriate and the procedure applying quality criteria to included studies are not explicitly clear in the MS. These factors limit the robustness of the systematic review.

- Despite no evidence to suggest that the statistical validity of the factorial approach was methodologically inappropriate, the validity of simply pooling data from essentially two different study designs (i.e. a two arm design and a 2x2 factorial design) without accounting for between study variability is inappropriate. Unweighted (for uncertainty) pooling of results from different studies is not advisable as there are almost certainly differences between trials and which, if not accounted for, are likely to lead to biased estimates of effect. The appropriateness of combining data from the two parts of the study was also questioned by the European Medicines Agency in their assessment of extending the licensed indication of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic carcinoma of the colon or rectum. The resulting pooled data (manufacturer's primary pooled analysis of superiority and non inferiority) should therefore be treated with caution.

1.4.3 Areas of uncertainty

- Although it is probable that the addition of bevacizumab to oxaliplatin-based chemotherapy increases progression free and overall survival, the size of the actual treatment effect of bevacizumab is uncertain, given the trial design limitations (two part

study, open label design, imbalance of known prognostic factor [time between primary treatment and recurrence] and relatively short duration of chemotherapy treatment (aproximately 6 months) despite the fact that the trial protocol allowed coninuation of the study therapy until progressive disease or unacceptable toxicity) and the interpretation of the statistical analyses (pooled analysis of all patients versus analysis by factorial design).

- There is uncertainty around whether bevacizumab treatment should be continued until progression of the underlying disease.

- The main areas of uncertainty within the cost-effectiveness analysis relate to the choice of efficacy and health related quality of life (HRQoL) data, and the differences in treatment duration and continuity between the trial and clinical practice.

1.5 Key issues

A number of issues were identified that had an impact on the ICERs. These included the following:

- Avastin Patient Access Scheme (APAS): At the time of writing the decision on whether the proposed APAS scheme would be accepted was unknown. The majority of the analysis presented by the manufacturer included the APAS. Running the model without the APAS resulted in much higher ICERs.

- Efficacy data: It is unclear whether the clinical evidence from the randomised controlled trial used in the MS should be pooled (without weighting for uncertainty) according to data from the initial two arm part and the 2x2 factorial part of the NO16966 study or restricted to patients in the 2x2 factorial part, as per the original statistical trial plan of the NO16966 trial. Additionally it is unclear whether patients with prior adjuvant chemotherapy should be excluded from the analysis. The restriction to the trial data from the 2x2 part of the NO16966 study, the unpooling of the XELOX and FOLFOX arms, and the restriction to the data of patients without prior adjuvant chemotherapy, all have a large impact on the resulting ICERs. The restriction of the analyses to the 2x2 part of the N016966 trial increased the ICERs, exclusion of patients with prior adjuvant chemotherapy decreased the ICERs, and pooling the XELOX and FOLFOX arms affected the XELOX and FOLFOX ICERs in different directions.

- HRQoL data: The MS does not make use of the range of utility values identified from the literature review and do not explain why these values were not used. The sources of the

utility values used in the MS were poorly referenced resulting in the ERG being unable to verify them. There is also uncertainty around the clinical plausibility of the post treatment pre-progression utility value. The distributions used for the utility values in the probabilistic sensitivity analyses (PSA) reflect the uncertainty relating to the specific values used but underestimate the uncertainty relating to the selection of utility values. Using wider distributions for utility values would significantly increase the confidence intervals around the mean ICERs from the PSA. Reducing the utility values by 20% markedly increased the ICERs.

- Treatment duration: In clinical practice, treatment with non-oxaliplatin chemotherapy components may continue beyond oxaliplatin cessation although in the N016966 trial was rarely seen. Due to the structure of the Avastin Patient Access Scheme (APAS) (in which oxaliplatin is received free of charge) this could have a significant impact on the ICERs. The ERG ran an exploratory analysis to determine the effect on the ICER of stopping oxaliplatin only one month earlier and assuming incremental effectiveness is unchanged. This exploratory analysis markedly increased the ICERs.

- Intermittent versus continuous chemotherapy: Current care in England is often intermittent treatment with chemotherapy. The trial and the model both represent continuous treatment chemotherapy. The difference in cost and effectiveness between intermittent and continuous treatment is unclear. As an example, if intermittent treatment was cheaper than continuous treatment whilst having a similar efficacy, then the ICER for continuous treatment with bevacizumab versus intermittent treatment would be greater than the ICERs for continuous treatment with bevacizumab versus continuous treatment.

2. BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem is brief and fairly accurate. However, the manufacturer's discussion of context (p24-31, MS) lacks detail on the epidemiology (incidence and/or prevalence), aetiology, and prognosis (staging and overall survival rates) of (metastatic) colorectal cancer.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is adequate although some discussion around specific points is required.

The MS (p25, 107-108) contains the results of the manufacturer's market research to determine the usage of chemotherapy by regimens and line (first, second or third) in the NHS in England and Wales. Limited data was provided however, the manufacturer failed to provide a detailed description of the methods undertaken for the market research. The ERG do not have experience of critically appraising market research data, and are not aware of any standard methodology doing this. The ERG's clinical advisors, however, indicated that the results of the market research data appear to be representative of first line treatment of metastatic colorectal cancer in England.

The MS (p30) suggest that patients currently receiving first line chemotherapy with fluoropyrimidine alone (5-fluorouracil plus folinic acid or capecitabine monotherapy) or fluoropyrimidine plus irinotecan are deemed unsuitable for more aggressive combination chemotherapy with oxaliplatin. However, the ERG's clinical advisors indicated that aggressive combination therapy with oxaliplatin may be used as a suitable treatment option at reduced doses or a 'stop and go' management approach may be taken.

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem addressed by the MS is shown in Table 1.

Table 1: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable	The UK Marketing Authorisation permits bevacizumab use with oxaliplatin-based chemotherapy at any line of therapy. However, the manufacturer will be seeking a positive recommendation for these combinations in first-line only.
Intervention	Bevacizumab in combination with oxaliplatin and either 5-fluorouracil or capecitabine	Bevacizumab in combination with oxaliplatin and either 5-fluorouracil or capecitabine
Comparator(s)	• Oxaliplatin-including chemotherapy regimens without bevacizumab • Irinotecan-including chemotherapy regimens without bevacizumab	**Primary analysis** Oxaliplatin-including chemotherapy regimens without bevacizumab **Secondary analyses** Irinotecan-based regimens are considered of limited clinical relevance. However, for completeness an economic comparison has been performed versus irinotecan-based therapy, given there may be a small number of patients for whom this comparison is relevant
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	The outcome measures considered included: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life
Economic Analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services

	Final scope issued by NICE	Decision problem addressed in the submission
	perspective.	perspective.
Subgroups to be considered	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows the appraisal should consider the use of continuation rules based on tumour response	Consideration will be given to the activity of bevacizumab in patients with isolated liver metastases because the recent cetuximab guidance from NICE has defined this as a group where different approaches to drug therapy may be required.

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as 'people with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable.' Although the term 'suitable' was not defined in the NICE scope, the MS (p26) suggest that this patient population would include people that are not resistance to adjuvant oxaliplatin (i.e. having progressed during or soon after stopping oxaliplatin-based adjuvant therapy or in those patients for whom oxaliplatin is contraindicated e.g. pre-existing neuropathy). In addition, the MS does not include any details on the mean age at diagnosis in the UK against which to compare the characteristics of patients in the clinical trial.

3.2 Intervention

Bevacizumab is a recombinant humanised monoclonal antibody that inhibits the action of vascular endothelial growth factor (VEGF), by binding to receptors on endothelial cells and thereby neutralising the physiological activity of VEGF. This reduces development of blood vessels within tumours and inhibits tumour growth.

Bevacizumab is currently licensed in the EU (including the UK) in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic carcinoma of the colon or rectum. The licensed dose, administered by intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every two weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every three weeks. The ERG note that the clinical efficacy of the higher licensed dose has not been demonstrated in a randomised clinical trial of patients with metastatic colorectal cancer.[1]

Additional licensed indications (not the subject of this appraisal) to the products market authorisation include the following:

- bevacizumab in combination with paclitaxel or docetaxel is indicated for first-line treatment of patients with metastatic breast cancer;
- bevacizumab in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology and
- bevacizumab in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

3.3 Comparators

The decision problem addressed in the MS states that the standard comparator considered was oxaliplatin-including chemotherapy regimens without bevacizumab (primary analysis). However, the final scope issued by NICE states that comparisons should be made with (1) oxaliplatin-including chemotherapy regimens without bevacizumab (2) irinotecan-including chemotherapy regimens without bevacizumab

The manufacturer's decision to include oxaliplatin-including chemotherapy regimens without bevacizumab as the main comparator was based on evidence from market research data undertaken in December 2008, which suggests (p25, 108, MS) that oxaliplatin-based therapies are the most commonly used chemotherapy regimens for the first-line treatment of metastatic colorectal cancer in England (28% FOLFOX [intravenous 5-fluorouracil plus folinic acid plus oxaliplatin] and 24% XELOX [oral capecitabine plus intravenous oxaliplatin]). The MS (p13-16, 25, 108) states that a comparison with irinotecan-based chemotherapy regimens was considered of limited clinical and economic relevance because it is not commonly used within the UK (12% FOLFIRI [intravenous 5-fluorouracil plus folinic acid plus irinotecan] and 4% XELIRI [oral capecitabine plus irinotecan]) and is largely restricted to patients where oxaliplatin is contraindicated. In addition, approximately 25% of patients receive fluoropyrimidine monotherapy (capecitabine, 21%; intravenous 5-florouracil plus folinic acid, 4%) first-line for metastatic disease. These patients are those where the clinician and/or patient take the view that the additional toxicity conferred by oxaliplatin or irinotecan is unacceptable. The manufacturer

considered this patient population to be outside the scope of this appraisal, which is concerned with patients for whom oxaliplatin-based chemotherapy regimens would be suitable.

Although the ERG acknowledges that oxaliplatin-based chemotherapy regimens without bevacizumab are the most potentially relevant comparators for all patients with metastatic colorectal cancer, it also considers irinotecan-based chemotherapy regimens as potentially relevant comparators. The use of this treatment is also advocated by current NICE guidance which recommends FOLFIRI as a first-line treatment option for metastatic colorectal cancer.[2] While the systematic review undertaken in the MS did not consider irinotecan based chemotherapy regimens as a relevant comparator, the manufacturer undertook an economic evaluation with irinotecan-based chemotherapy (given the small number of patients for whom this comparison is relevant) for completeness.

3.4 Outcomes

The NICE scope outlines five clinical outcome measures and one measure of cost-effectiveness. All of these are stated to have been addressed in the MS (p13-15). Clinical outcome measures included overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life (HRQoL). These are all appropriate and clinically meaningful outcomes, and there are no other valid outcomes which the ERG would have expected to be included. Incremental cost per quality adjusted life years (QALYs) gained was used as a measure of cost-effectiveness, which is in accordance with the NICE reference case.[3]

3.5 Time frame

The manufacturer's time horizon in the health economic model was eight years. The MS (p109) states that this is equivalent to a life time horizon in the population of interest. The ERG acknowledges that the time horizon is appropriate with less than 0.1% of the population being alive at the end of eight years.

3.6 Other relevant factors

While the UK marketing authorisation does not specify a line of treatment for the use of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of

patients with metastatic colorectal cancer, the manufacturer is seeking approval for first-line use only (p13, MS). Although randomised clinical trial evidence is available to support the use of bevacizumab in combination with an oxaliplatin containing regimen as a second-line therapy (relapsed disease) for metastatic colorectal cancer, the MS states (p13, 27, 106) that it is not proposing second-line use because a preliminary analysis of cost-effectiveness indicated that second-line use of bevacizumab, at the dose tested in the E3200 trial[4] (twice that proposed for first-line use) would not meet NICE's cost-effectiveness thresholds. Therefore the manufacturer would not be able to demonstrate a case for bevacizumab in this setting. The ERG acknowledges that the manufacturer has provided the wider evidence base for bevacizumab from the E3200 trial in the MS for completeness but is not the focus of the submission.

The final scope issued by NICE states that if evidence allows the appraisal should consider the use of continuation rules based on tumour response (the ERG notes that this is absent in the manufacturers statement of the decision problem). The MS (p105) states that the summary of product characteristics for bevacizumab recommends treatment to be continued until progression of the underlying disease. However, the economic analysis is based on the observed treatment duration in the NO16966 study,[5] where the average treatment duration was less than the time to progression (i.e. treatment with bevacizumab was often stopped at the same time-point as the base chemotherapy was stopped). The economic model is an accurate representation of treatment duration as it occurred in the trial but there is reason to believe that a longer duration of treatment with bevacizumab and 5-fluorouracil may be seen in clinical practice. A longer duration of treatment would significantly increase incremental costs and may also increase survival times. The ERG is unclear of the treatment effect and cost effectiveness if bevacizumab is provided as per the summary of product characteristics recommendations.

No other relevant subgroup analyses are explicitly stated in the final scope issued by NICE. However, in the manufacturers definition of the decision problem (p14, MS), it is stated that consideration will be given to the activity of bevacizumab in patients with isolated liver metastases because the NICE guidance on cetuximab defined this as a group where a different approach to drug therapy may be required.[6] Although this post-hoc subgroup analysis has been considered in the MS (p71), the ERG notes that the coverage is inadequate, as the results (including reference sources) have been poorly reported. An evaluation of the cost effectiveness of adding bevacizumab to oxaliplatin-based chemotherapy in patients with liver metastases was not undertaken by the manufacturer, despite an ERG request.

Bevacizumab is a fixed cost per cycle through the APAS. This is £800 and £1200 per 2 weekly and 3 weekly cycles respectively. The cost of bevacizumab is free after 1 year and oxaliplatin is provided free for all patient registered with the APAS receiving bevacizumab.

4. CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The search strategies supplied reflect a reasonable attempt to identify the literature relating to bevacizumab and its use in colorectal cancer. All the required databases have been searched (although the strategy for the Cochrane Controlled Trials Register [CCTR] is missing, and therefore was not re-run for this report). The search strategies supplied for BIOSIS, MEDLINE and EMBASE were from the Dialog system. Due to access restraints, these were re-run by the ERG in the OVID and ISI Web of Science system. Although there were some significant differences between the number of search results found by the ERG compared with those reported in the MS, in most cases this is likely due to differences in searching between the two systems and the time lag between the searches being conducted and tested. Also the ERG was unable to re-run the search on the Health Economics Evaluation Database (HEED) as the ERG do not have access to this database.

However, the search strategies seem to show some inconsistencies and are occasionally meandering, with terms appearing in the search history which are never combined or incorporated into the main search strategy and with no evidence that they have even been tested with other terms to see how their inclusion might have affected the overall result. For example in the MEDLINE Economics search strategy the terms *cost.mp, economic.mp, (health adj technology adj appraisal).mp and (colorectal adj cancer).mp* are all listed but never incorporated into the rest of the search strategy. The drug itself is not fully explored, with the alternative term *Avastin* notable by its absence. The overall appearance of the searches is one of specificity not sensitivity – for example in the MEDLINE clinical effectiveness strategy the term *bevacizumab* is combined using the boolean operator AND with the MESH term **antibodies, monoclonal/* - presumably to limit the number down to the most relevant papers but given the very small number of papers published this seems somewhat counter-productive. The searches might have benefited from a broader approach and the application of published methodological filters to identify utility/economics data.[7]

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The MS describes an inappropriate method of identifying and screening references for inclusion in the systematic review. The MS (provided as supplementary data) states that data selection and abstraction was undertaken by one individual. To ensure reproducibility and minimize selection bias assessment of eligibility of studies, and extraction of data from study reports, should be done by at least two people, independently.[8]

Details of the inclusion and exclusion criteria, as specified in the MS (p40) and that provided as supplementary data, for the systematic review of the literature is summarised in Table 2.

Table 2: Inclusion/exclusion criteria in the MS study selection

Criteria	Clinical effectiveness
Inclusion	• Population Patients with metastatic colorectal cancer • Intervention Oxaliplatin-based chemotherapy plus bevacizumab • Comparator Oxaliplatin-based chemotherapy without bevacizumab

The specified inclusion criteria are (mostly) appropriate and generally reflect the information given in the decision problem; however, there appears to be some irregularities and ambiguities in the MS.

The MS does not explicitly report any inclusion criteria relating to the study design, outcomes of interest or publication type. The ERG assumes that the review of clinical effectiveness was limited to phase III randomised controlled trials only and excluded non-English language papers and non-human studies. Although the MS included non-randomised studies (which were identified via the original searches or known to the manufacturer's information expert), it is unclear if any additional literature searches were undertaken to identify non-randomised studies. In addition, the MS did not state whether published systematic reviews and meta-analysis of primary studies would be considered in the review. The identification and assessment of such

studies would have been useful to identify any additional studies not identified by the literature searches.

The decision problem addressed in the MS states that the UK marketing authorisation permits the use of bevacizumab in combination with oxaliplatin-based chemotherapy for the treatment of patients with metastatic colorectal cancer at any line of therapy. Whilst this appears to be the approach for the systematic review in the MS (p33-73), the manufacturer is seeking approval of bevacizumab for first-line use only (Title page, p13, MS). The ERG believes the systematic review of clinical effectiveness should be a clearly defined focused review on first-line use only, with additional supportive evidence presented for other lines of therapy, for completeness.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded

The MS identified two, head-to-head, phase III, randomised, active-controlled trials that investigated the addition of bevacizumab to an oxaliplatin-containing regimen, one as first-line therapy (patients not previously treated for their metastatic disease, NO16966 trial)[5] and one in second-line therapy (for previously treated patients with metastatic disease, E3200 trial).[4] Details of the study design and patient characteristics are summarised in Table 3.

The MS (p41-42, 84-96) also identified one non-randomised study (Three Regimens of Eloxatin Evaluation [TREE] study)[9] and two phase IV observational studies (The Bevacizumab Expanded Access Trial, BEAT[10] and the Bevacizumab Regimens: Investigation of Treatment Effects and Safety, BRiTE)[11] that provided additional data on the efficacy and safety of bevacizumab. The manufacturer (p42, MS) states that they are not aware of any relevant ongoing studies of bevacizumab combined with oxaliplatin-based chemotherapy.

Although no evidence synthesis in the form of a meta-analysis or multiple treatment comparison analyses was undertaken by the manufacturer (further discussion is provided in section 4.1.7 and 4.2.2), additional evidence from a meta-analysis of randomised controlled trials comparing the efficacy and safety of chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer[12] and a mixed treatment comparison analyses of survival and disease progression

benefits with different treatment regimens (including bevacizumab plus oxaliplatin or irinotecan for first-line and /or non-first-line treatment) for advanced colorectal cancer[13] was also identified (p73-77, MS).

The manufacturer's QUORUM diagram (provided as supplementary evidence) relating to the literature searches conforms to the QUORUM statement flow diagram (www.consort-statement.org); however, the MS does not provide a full and explicit breakdown of the reasons why all citations were rejected, especially after full text papers were retrieved for detailed evaluation (reasons for exclusion for some full text papers were reported).

Table 3: Characteristics of included studies

Study	Design	Participants (inclusion criteria)	Interventions [a,b]	Outcomes	Follow up
NO16966 trial[5]	Phase III, multicentre, multinational (32 countries including the UK), randomised, active controlled trial (Two part study - Part 1: initial two-arm open label study and Part 2 [after protocol amendment]: 2x2 factorial, double blind [for bevacizumab], active-placebo controlled trial)	Adults (male and female ≥18 years of age with Eastern Cooperative Oncology Performance Status of 0 or 1) with histologically confirmed, metastatic adenocarcinoma of the colon or rectum, not previously treated (no prior systemic therapy for advanced colorectal cancer - first-line treatment)	Part 1: Initial two arm T1': XELOX (n=317) T2': FOLFOX-4 (n=317) Part 2: 2x2 factorial, four arm T1: B-XELOX (n=350) T2: B-FOLFOX-4 (n=350) T3: P-XELOX (n=350) T4: P-FOLFOX-4 (n=351)	Co-Primary study endpoints The co-primary study endpoints after protocol modification were: • Superiority of progression free survival in patients receiving chemotherapy (B-XELOX/B-FOLFOX-4) is superior to chemotherapy alone (P-XELOX/P-FOLFOX-4) • Non-inferiority of progression free survival in patients receiving XELOX with or without bevacizumab is equivalent to FOLFOX-4 with or without bevacizumab Secondary endpoints • Progression free survival for superiority of XELOX over FOLFOX • Overall Survival • Overall Rate of Best Response • Time to Response • Duration of Response • Duration of Complete Response • Time to Treatment Failure • Safety	Median 28 months
E3200 trial[4]	Phase III, multicentre (220 sites in the USA), randomised, open-label controlled trial	Adults (male and female ≥18 years of age with Eastern Cooperative Oncology Performance Status of 0 to 2) with histologically confirmed, advanced or metastatic adenocarcinoma of the colon or rectum previously treated (second-line treatment) with fluoropyrimidine and irinotecan based regimens (either	T1: B-FOLFOX (n=293) T2: FOLFOX-4 (n=292) T3: B alone (n=244) (recruitment to T3 terminated at interim efficacy analysis after survival determined to be inferior)	Primary study endpoint • Overall survival Secondary endpoints • Response Rate • Progression free survival) • Duration of response. • Safety	Median 28 months

Study	Design	Participants (inclusion criteria)	Interventions [a,b]	Outcomes	Follow up
		separately or in combination for advanced disease)			

[a,] All treatment regimens (scheduled to receive at least 48 weeks of treatment in the NO16966 trial or) were continued until disease progression or unacceptable toxicity

[b] Individual regimens are as follows

XELOX regimen: XELOX consisted of a 2 hour intravenous infusion of oxaliplatin 130mg/m^2 on day 1 followed by oral capecitabine 1000mg/m^2 twice daily on days 1 through 14 (28 doses) of a 21 day cycle.

FOLFOX-4 regimen: FOLFOX-4 consisted of folinic acid given at a dose of 200 mg/m^2/day followed by bolus 5- fluorouracil 400 mg/m^2 and a 22 hour infusion of 5-fluorouracil 600 mg/m^2 for two consecutive days. Oxaliplatin was administered on day 1 at the dose of 85 mg/m^2 as a 2 hour infusion, concurrently with folinic acid. The treatment was repeated every 2 weeks (14 day cycle).

P-XELOX regimen: Placebo was administered as a 30 to 90 minute intravenous infusion before oxaliplatin at a dose of 7.5mg/kg on day 1 of a 21 day cycle when given with XELOX

B-XELOX regimen: Bevacizumab was administered as a 30 to 90 minute intravenous infusion before oxaliplatin at a dose of 7.5mg/kg on day 1 of a 21 day cycle when given with XELOX

P-FOLFOX-4 regimen: Placebo was administered as a 30 to 90 minute intravenous infusion before oxaliplatin at a dose of 5mg/kg on day 1 of a 14 day cycle when given with FOLFOX-4

B-FOLFOX-4 regimen: Bevacizumab was administered as a 30 to 90 minute intravenous infusion before oxaliplatin at a dose of 5mg/kg (in the NO16966 trial) or 10mg/kg (in the E3200 trial) on day 1 of a 14 day cycle when given with FOLFOX-4

B- alone: Bevacizumab was administered as a 30 to 90 minute intravenous infusion at a dose of 10mg/kg on day 1 of a 14 day cycle

4.1.4 Details of any relevant studies that were not included in the submission?

Although there were some significant differences between the repeat searches using the manufacturer's search terms compared to those reported in the MS, it is very likely (in most cases) due to differences in searching between the different systems (manufacturer used the Dialog system whereas the ERG used the OVID and ISI Web of Science systems) and the time lag between the searches being conducted and tested. The ERG is confident that all relevant studies were included in the MS and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.1.5 Description and critique of manufacturers approach to validity assessment

The validity assessment tool used in the MS is generally reflective of the quality assessment criteria developed by NICE.[14] However, it is not clear whether this was done by a single reviewer or consensus of multiple reviewers. The completed validity assessment tool for the two trials, as reported in the MS, is reproduced (with minor changes) in Table 4. The ERG acknowledges that the validity assessment tool used in the MS was appropriate.

The majority of the data for the validity assessment appears to be derived from the trial protocol (which was not requested by the ERG) and is not published in the peer reviewed articles. As a result, it was not possible for the ERG to check the validity of the manufacturer's quality assessment; however some further discussion around specific points is required.

Table 4. Validity assessment of completed trials included by the manufacturer

Validity assessment	Trials	
	Primary study NO16966	**Supportive study ECOG E3200**
How was allocation concealed?	In the assessment of bevacizumab efficacy a matched placebo was used to which patients and investigators were blind. For the comparison of oral capecitabine and intravenous 5-fluorouracil, placebo control was impractical and unethical (widespread use of intravenous placebo). Therefore, patients and clinicians were unblinded to treatment allocation. However, primary end-point was objective (tumour shrinkage on a scan) and the investigator assessment of response was checked using radiologists blind to treatment allocation	This was an open label study. However, the primary study end-point of overall survival is not liable to investigator bias
What randomisation technique was used?	Acceptable. Centralised, using interactive voice recognition system (adaptive randomisation)	Acceptable, based on limited information Centralised by the Eastern Cooperative Oncology Group Co-ordinating Centre
Was follow-up adequate?	Yes. Analyses for primary end-point (progression free survival) and overall survival was event-driven as specified in the statistical plan.	Yes. Study was stopped at a protocol specified interim analysis which demonstrated that (as specified in the trial statistical analysis plan) the O'Brien-Fleming boundary for the primary end-point had been crossed with alpha controlled at 0.00167. A final analysis for survival was subsequently conducted when 91% of FOLFOX and 89% of B-FOLFOX patients had died with a median follow-up of 25.0 and 28 months, respectively.
Were the individuals undertaking the outcomes assessment aware of allocation?	The primary analysis was based on investigator assessment of progression free survival. Investigators were blinded to treatment allocation of bevacizumab or placebo, but not to the allocation of XELOX versus FOLFOX. A supportive analysis conducted by independent reviewers blind to all treatment allocation was conducted.	No, but this was irrelevant to the primary end-point in this study (overall survival)
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from	This was a multinational study conducted by 216 investigators from 32 countries including the UK. The principal investigator on the study was Prof James Cassidy from the Beatson Oncology Centre in Glasgow. Clearly Prof Cassidy felt that the	No. This study was conducted in the USA. The main difference between the study population in the USA and the UK is probably in the first-line treatment that they received. In the UK, the predominant first-line chemotherapy is oxaliplatin plus a