

The clinical effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal No. 150 and part review of technology appraisal No. 118): a systematic review and economic model

M Hoyle,^{1*} L Crathorne,¹ J Peters,¹ T Jones-Hughes,¹
C Cooper,¹ M Napier,² P Tappenden³ and C Hyde¹

¹Peninsula Technology Assessment Group (PenTAG), University of Exeter, Exeter, UK

²Royal Devon & Exeter Foundation Trust Hospital, Exeter, UK

³School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK

*Corresponding author



Executive summary

Cetuximab, bevacizumab and panitumumab for metastatic colorectal cancer

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Executive summary

Background

Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). It is the third most commonly diagnosed cancer in the UK after breast and lung cancer. In 2008 there were 39,991 new cases of large bowel cancer registered in the UK, around two-thirds (25,551) in the colon and one-third (14,440) in the rectum. Colorectal cancer was the second most common cause of cancer death (10%) after lung cancer in the UK in 2006 [Cancer Research UK. *Bowel (colorectal) cancer – UK incidence statistics*; 2011. URL: <http://info.cancerresearchuk.org/cancerstats/types/bowel/incidence> (accessed 10 March 2011)]. In total, there were 16,259 deaths from colorectal cancer: 10,164 from colon cancer and 6095 from rectal cancer [Cancer Research UK. *Bowel (colorectal) cancer – mortality statistics*; 2011. URL: <http://info.cancerresearchuk.org/cancerstats/types/bowel/mortality/> (accessed 10 March 2011)].

In metastatic colorectal cancer the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body. This is described as stage IV of the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system or stage D of the modified Dukes' classification. The 5-year survival of patients with advanced disease (modified Dukes' D) is < 7% [Cancer Research UK. *Bowel (colorectal) cancer – survival statistics*; 2011. URL: <http://info.cancerresearchuk.org/cancerstats/types/bowel/survival/> (accessed 10 March 2011)].

Individuals with metastatic disease who are sufficiently fit (normally those with World Health Organization performance status ≤ 2) are usually treated with active chemotherapy as first- or second-line therapy. First-line active chemotherapy options include:

- infusional 5-fluorouracil plus folinic acid (5-FU/FA)
- oxaliplatin plus infusional 5-FU/FA (FOLFOX)
- irinotecan plus infusional 5-FU/FA (FOLFIRI)
- oral analogues of 5-FU (capecitabine and tegafur with uracil) may also be used instead of infusional 5-FU.

More recently, targeted agents have become available including anti-epidermal growth factor receptor (EGFR) agents, for example cetuximab and panitumumab, and anti-vascular endothelial growth factor (VEGF) receptor agents, for example bevacizumab. The EGFR signalling pathway has been the focus of new drug development for colorectal cancer because it is overexpressed in approximately 80% of colorectal carcinomas. Kirsten rat sarcoma (KRAS) mutation status – wild type (WT) or mutant – can explain resistance to anti-EGFR therapy.

A treatment algorithm for colorectal cancer in England and Wales developed by Tappenden and colleagues (technology appraisal No. 118) estimated that up to 85% of patients with advanced metastatic colorectal cancer not amenable to resection receive active first-line therapy [Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. *Health Technol Assess* 2007;**11**(12)]. Of these, approximately 50% go on to receive second-line therapy with 5% of those estimated to go on to receive third-line therapy. This treatment algorithm showed that roughly 300 patients receive a third-line chemotherapy in England and Wales.

The National Institute for Health and Clinical Excellence (NICE) currently recommends FOLFOX and FOLFIRI as first-line treatment options for advanced colorectal cancer. FOLFOX or irinotecan alone are recommended as subsequent therapy options. The oral analogues of 5-FU, capecitabine and tegafur, in combination with uracil (and FA) are also recommended as first-line treatment options for

metastatic colorectal cancer. Cetuximab in combination with FOLFOX, or in combination with FOLFIRI, is recommended as an option for the first-line treatment of metastatic colorectal cancer when the metastatic disease is confined to the liver and the aim of treatment is to make the metastases resectable. In technology appraisal No. 118, bevacizumab in combination with 5-FU/FA, with or without irinotecan, as a first-line treatment and cetuximab in combination with irinotecan as a second- or subsequent-line treatment were not recommended for metastatic colorectal cancer. Technology appraisal No. 150 on cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy in 2008 was terminated because the manufacturer submitted a 'no evidence' response to NICE [National Institute for Health and Clinical Excellence. *Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy*. TA150 (terminated appraisal). London: NICE; 2008].

This technology assessment report considered three pharmaceutical interventions: bevacizumab (Avastin[®], Roche), cetuximab (Erbix[®], Merck Serono) and panitumumab (Vectibix[®], Amgen). All three have UK marketing authorisation:

- bevacizumab is licensed in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer
- cetuximab is licensed for the treatment of patients with EGFR-expressing metastatic colorectal cancer with *KRAS* WT status either in combination with chemotherapy or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan
- panitumumab is licensed for the treatment of EGFR-expressing metastatic colorectal cancer with *KRAS* WT status after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

The following question was addressed by this report: 'What is the clinical effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy'.

The main comparators of interest are irinotecan- or oxaliplatin-based chemotherapy regimens and best supportive care. The populations of interest were limited to metastatic colorectal cancer patients with *KRAS* WT status in the case of cetuximab and panitumumab.

Methods

The assessment comprises a systematic review of clinical effectiveness and cost-effectiveness studies, a review and critique of manufacturer submissions and a de novo economic analysis.

Clinical effectiveness systematic review

For the assessment of effectiveness, a literature search was conducted in a range of electronic databases including MEDLINE, EMBASE and The Cochrane Library (2005–17 November 2010).

Studies were included if they were:

- RCTs or systematic reviews of RCTs of cetuximab, bevacizumab or panitumumab
 - in participants with EGFR-expressing metastatic colorectal cancer with *KRAS* WT status that has progressed after first-line chemotherapy (for cetuximab and panitumumab)
 - in participants with metastatic colorectal cancer that has progressed after first-line chemotherapy (for bevacizumab).

All steps in the review were performed by one main reviewer and checked independently by a second. Quality was assessed using criteria specified by the Centre for Reviews and Dissemination (CRD). Synthesis was mainly narrative.

Cost-effectiveness systematic review

For the cost-effectiveness review, the inclusion and exclusion criteria were the same as for the clinical effectiveness review except for study design, with non-randomised studies, full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses included.

Review of manufacturers' submissions

The cost-effectiveness analyses reported in the manufacturers' submissions to NICE were critically appraised using established frameworks, including the NICE reference case.

Three manufacturers' submissions were potentially available for this appraisal; however, only one full economic model was submitted, by Merck Serono (the manufacturer of cetuximab), for cetuximab plus irinotecan and panitumumab plus best supportive care compared with best supportive care. Roche (the manufacturer of bevacizumab) submitted some basic cost calculations in its report for a comparison between bevacizumab plus FOLFIRI and cetuximab plus FOLFIRI. Amgen did not provide any details of a cost-effectiveness model, nor make any comment on the likely cost-effectiveness of panitumumab, its product.

Peninsula Technology Assessment Group cost-effectiveness analysis

A decision-analytic model was developed following the NICE reference case, from the perspective of the NHS and Personal Social Services (PSS).

The model focused on third- and subsequent-line treatment as agreed with NICE. The use of drugs of interest second line was theoretically covered by the scope, but there were no clinical effectiveness data, no case for such a comparison was made by the manufacturers and there was no obvious clinical case for such use. We did not model bevacizumab in combination with non-oxaliplatin-based chemotherapy because of the absence of clinical effectiveness data for this treatment.

The structure of the model is widely used for metastatic cancers. It uses an 'area under the curve' method to determine state probabilities at each cycle of the model. The model has three health states: progression-free survival, progressive disease and dead. We performed an indirect four-way comparison of the cost-effectiveness of best supportive care, cetuximab, panitumumab and cetuximab plus irinotecan.

The clinical effectiveness of best supportive care and cetuximab is taken from a RCT of cetuximab plus best supportive care compared with best supportive care, and of panitumumab is taken from a RCT of panitumumab plus best supportive care compared with best supportive care. Both of these RCTs were those identified in the systematic review (see *Results*). The clinical effectiveness of cetuximab plus irinotecan was derived from a RCT of cetuximab plus irinotecan compared with cetuximab in which information on *KRAS* status was not available.

Results

Number and quality of clinical effectiveness studies

The searches identified 7745 titles and abstracts. Two clinical trials (reported in 12 papers) were included. No data were available for bevacizumab in combination with non-oxaliplatin-based chemotherapy in previously treated patients. Neither of the included studies had *KRAS* status performed prospectively, but the studies did report retrospective analyses of the results for the *KRAS* WT subgroups. Taken as a whole, the quality of the included studies was considered good.

Summary of benefits and risks

Third-line treatment with cetuximab plus best supportive care or panitumumab plus best supportive care appears to have clinically relevant and statistically significant advantages over treatment with best supportive care alone in patients with *KRAS* WT status. In both trials, median progression-free survival almost doubles. For cetuximab plus best supportive care, median progression-free survival increases from approximately 2 months to approximately 4 months [hazard ratio 0.40, 95% confidence interval (CI) 0.30 to 0.54]. For panitumumab plus best supportive care, median progression-free survival increases from approximately 2 months to approximately 3 months (hazard ratio 0.45, 95% CI 0.34 to 0.59) (Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, *et al.* K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;**359**:1757–65; Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman D, *et al.* Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;**26**:1626–34).

For the *KRAS* WT population, median overall survival in the cetuximab arm is 9.5 months compared with 4.8 months for best supportive care (hazard ratio 0.55, 95% CI 0.41 to 0.75). The effect of panitumumab on overall survival is less convincing and not statistically significant. The median overall survival for panitumumab was 8.1 months compared with 7.6 months for best supportive care (hazard ratio 0.99, 95% CI 0.75 to 1.29). The rapid crossover of 76% of patients originally allocated to best supportive care to treatment with panitumumab (median time to crossover 7.1 weeks) is likely to have had an extensive confounding effect (Amado *et al.* 2008; Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, *et al.* Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;**25**:1658–64).

For both progression-free survival and overall survival the effects in patients with *KRAS* WT status are greater than those in the whole trial populations.

Number and quality of cost-effectiveness studies

Summary of economic evaluations

Our literature search identified five published full economic evaluations meeting the inclusion criteria. Three abstracts were also identified but these did not provide sufficient detail for a full critical appraisal.

All of the included studies assessed the cost-effectiveness of cetuximab used as third-line therapy (Annemans L, Van Cutsem E, Humblet Y, Van Laethem JL, Bleiberg H. Cost-effectiveness of cetuximab in combination with irinotecan compared with current care in metastatic colorectal cancer after failure on irinotecan – a Belgian analysis. *Acta Clin Belg* 2007;**62**:419–25; Mittmann N, Au HJ, Tu D, O'Callaghan CJ, Isogai PK, Karapetis CS, *et al.* Prospective cost-effectiveness analysis of cetuximab in metastatic colorectal cancer: evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 trial. *J Natl Cancer Inst* 2009;**101**:1182–92; Norum J. Cetuximab in the treatment of metastatic colorectal cancer: a model-based cost-effectiveness analysis. *J Chemother* 2006;**18**:532–7; Starling N, Tilden D, White J, Cunningham D. Cost-effectiveness analysis of cetuximab/irinotecan vs active/best supportive care for the treatment of metastatic colorectal cancer patients who have failed previous chemotherapy treatment. *Br J Cancer* 2007;**96**:206–12; Wong YN, Meropol NJ, Speier W, Sargent D, Goldberg RM, Beck JR. Cost implications of new treatments for advanced colorectal cancer. *Cancer* 2009;**115**:2081–91). However, only one of these, by Mittmann and colleagues, directly addressed a comparison of interest, cetuximab plus best supportive care compared with best supportive care, in the population of direct interest, metastatic colorectal cancer patients with *KRAS* WT status. The trial-based cost-effectiveness analysis (2007) calculated a cost per quality-adjusted life-year (QALY) of C\$186,761 (95% CI C\$130,326 to C\$334,940). Updating this to 2011, converting to pounds sterling and using the current UK price of cetuximab we estimated this to be approximately equivalent to £101,000 per QALY.

Industry submissions

Merck Serono (the manufacturer of cetuximab) focused its submission on third- and subsequent-line use and presented base-case incremental cost-effectiveness ratios (ICERs) of £47,000 per QALY gained for cetuximab plus best supportive care compared with best supportive care and £44,000 per QALY gained for cetuximab plus irinotecan combination therapy compared with best supportive care.

Our main critique of Merck Serono's model is that it underestimates the mean treatment duration leading to ICERs that are too low. Assuming that patients are treated for as long as they remain progression free (which we believe is a more realistic assumption) leads to much larger ICERs: £75,000 and £67,000 per QALY gained for cetuximab monotherapy compared with best supportive care and for cetuximab plus irinotecan combined therapy compared with best supportive care respectively.

We also believe that Merck Serono has underestimated the costs of best supportive care drug administration, leading us to the conclusion that more realistic ICERs from Merck Serono's model are around £82,000 and £75,000 per QALY gained for cetuximab plus best supportive care compared with best supportive care and for cetuximab plus irinotecan combined therapy compared with best supportive care respectively.

Roche (the manufacturer of bevacizumab) did not estimate cost-effectiveness but did present a case that, used second line, bevacizumab plus FOLFIRI would be less expensive than cetuximab plus FOLFIRI.

Amgen presented reasonable analyses to adjust for crossover in the study by Amado and colleagues (2008), leading to an adjusted estimate of overall survival advantage of 2.74 or 3.13 months, depending on the method of adjustment used, for panitumumab compared with best supportive care. Amgen did not present any estimates of cost-effectiveness.

De novo economic model results

Based on our degree of certainty of clinical effectiveness and mean treatment duration, we estimate that the cost-effectiveness of:

- cetuximab compared with best supportive care is £98,000 per QALY gained and is reasonably accurate
- panitumumab compared with best supportive care is £150,000 per QALY gained and is reasonably accurate
- cetuximab plus irinotecan compared with best supportive care is £88,000 per QALY gained but is highly uncertain.

The incremental costs and QALYs for cetuximab and panitumumab compared with best supportive care are similar (approximately £25,000 and 0.20 QALYs per person), whereas these quantities are both far greater for cetuximab plus irinotecan compared with best supportive care (approximately £53,000 and 0.60 QALYs per person).

The probability that the three treatment regimens are cost-effective compared with best supportive care, up to a willingness-to-pay threshold of £60,000 per QALY, is zero.

The deterministic sensitivity analysis suggests that progression-free survival, overall survival, time on drug treatment, drug acquisition costs and drug administration costs strongly influence cost-effectiveness estimates.

Discussion

Strengths and limitations of the systematic review of effectiveness studies

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a prespecified protocol. The main limitation was lack of evidence on bevacizumab, cetuximab and cetuximab plus irinotecan used second line in the populations of interest and lack of evidence on bevacizumab and cetuximab plus irinotecan used third line.

Strengths and limitations of the systematic review of cost-effectiveness studies

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a prespecified protocol. The main limitation was the incomplete reporting of the cost-effectiveness of panitumumab and the absence of cost-effectiveness estimates for bevacizumab.

Strengths and limitations of the critique of industry submissions

This was conducted by an independent research team using a number of established frameworks to identify strengths and weaknesses. The scope of the submissions on bevacizumab and panitumumab, which did not directly estimate cost-effectiveness, was the main limitation.

Strengths and limitations of the economic modelling by the Peninsula Technology Assessment Group

Strengths

Our assessment of the cost-effectiveness of drugs for metastatic colorectal cancer is independent. Our analysis is the second independent fully published cost-effectiveness analysis of cetuximab compared with best supportive care for patients with *KRAS* WT status, the first being that of Mittmann and colleagues (2009), and the first specifically for the UK. Our analysis is the first independent fully published cost-effectiveness analysis of panitumumab compared with best supportive care for patients with *KRAS* WT status and of cetuximab plus irinotecan compared with best supportive care for patients with *KRAS* WT status. We have carefully compared our model and the results of our analysis with those of Mittmann and colleagues and Merck Serono, and in doing so we have highlighted areas in common and those where there is disagreement.

Our certainty about the accuracy of our cost-effectiveness results for cetuximab compared with best supportive care and panitumumab compared with best supportive care is increased given that the effectiveness evidence that underpins these analyses is taken from high-quality RCTs whose data are mature. There is much greater uncertainty concerning the analysis for cetuximab plus irinotecan compared with best supportive care given the lack of effectiveness evidence, particularly for patients with *KRAS* WT status.

We have confidence in the accuracy of our utility estimates for the best supportive care, panitumumab and cetuximab treatment arms. Indeed their accuracy is greater than is typically available for cost-effectiveness analysis, being derived from direct observation of patients in trials. This is not true for the utilities for cetuximab plus irinotecan.

Limitations

Some factors limit the accuracy of our analysis. For example, the mean duration of drug treatment for patients with *KRAS* WT status, a vital parameter, is available in published form only for panitumumab, although we have been told the mean duration of cetuximab monotherapy by personal communication. These are important limitations in the evidence for our analysis given that cost-effectiveness is very sensitive to these parameters.

The external validity of the results is uncertain given that we use efficacy data from RCTs in which patients are relatively young (median age approximately 63 years) and fit [Eastern Cooperative Oncology Group (ECOG) score 0–2], compared with people in actual clinical practice who are typically older and less fit (some with ECOG score 3–4).

Progression-free survival and overall survival for cetuximab plus irinotecan are available only for all patients combined: *KRAS* WT and *KRAS* mutant status. Like Merck Serono we have therefore been forced to adjust these estimates using other data sources to obtain estimates of progression-free survival and overall survival in patients with *KRAS* WT status. However, we have provided several possible methods of adjustment and the ICER for cetuximab plus irinotecan compared with best supportive care remains high regardless of which estimates for progression-free survival and overall survival are used.

In common with Merck Serono we do not stratify our analysis according to the line of treatment as the necessary individual patient data were not available.

We estimate the cost of medical management in progressive disease for all treatment groups based on a study of medical management in progressive disease for women with breast cancer (Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Br J Cancer* 2004;**91**:77–83). Like Merck Serono we believe that this is methodologically acceptable given the absence of suitable alternatives, but do caution that the data from this publication are now rather old, relating to practices from 2000.

Main findings in the light of strengths and limitations

Clinical effectiveness

There is no consensus about the evidence on the effectiveness of cetuximab and panitumumab for patients with *KRAS* WT status. Based on RCTs, both cetuximab and panitumumab are effective used third line, particularly with respect to progression-free survival. We broadly agree with Merck Serono's estimates of the effectiveness of cetuximab plus irinotecan for patients with *KRAS* WT status even though it has not been directly measured in a RCT. There is an absence of RCT evidence of bevacizumab combined with non-oxaliplatin chemotherapy in second and further lines of therapy.

Cost-effectiveness of cetuximab plus best supportive care

There are many similarities between Merck Serono's cost-effectiveness model for cetuximab compared with best supportive care and the Peninsula Technology Assessment Group's (PenTAG) de novo model. Importantly, we assume the same mean times as Merck Serono for progression-free survival and overall survival for cetuximab and for best supportive care. Nonetheless, Merck Serono estimates a far lower ICER than us for cetuximab compared with best supportive care: £47,000 compared with £98,000 per QALY gained. This is explained almost entirely by Merck Serono's estimates of the total mean costs of cetuximab acquisition and administration, which are far lower than our estimates. These differences in turn are due almost entirely to Merck Serono's far lower estimate of the mean time on cetuximab treatment: 2.6 months compared with 4.8 months. Merck Serono's derivation of its estimate is based on its imposition of an artificial maximum time on cetuximab treatment. When we use Merck Serono's model, and lift its cap on the time on cetuximab treatment, the ICER increases from £47,000 to £75,000 per QALY gained.

We are aware of only one other fully published cost-effectiveness analysis of any of the treatments in this appraisal for patients with *KRAS* WT status, that of Mittmann and colleagues (2009). They perform a trial-based economic analysis to consider cost-effectiveness from the health-care payer perspective in Canada. After we adjust their result for the cost per mg of cetuximab appropriate in the UK in 2011, and other costs for inflation to the year 2011, we estimate that their ICER is approximately equivalent to £101,000 per QALY gained. This is very close to our estimate of £98,000 per QALY gained and much higher than Merck Serono's £47,000 per QALY gained.

Cost-effectiveness of cetuximab plus irinotecan compared with best supportive care

Again, there are many similarities between Merck Serono's model for cetuximab plus irinotecan compared with best supportive care and the PenTAG de novo model. Importantly, we assume similar mean times as Merck Serono for progression-free survival and overall survival for cetuximab plus irinotecan and for best supportive care. Merck Serono estimates a far lower ICER than us for cetuximab plus irinotecan compared with best supportive care: £44,000 compared with £88,000 per QALY gained. Similar to the case of cetuximab compared with best supportive care, this is explained almost entirely by Merck Serono's estimates of the total mean costs of cetuximab plus irinotecan acquisition and administration, which are far lower than our estimates. These differences, in turn, are due almost entirely to Merck Serono's far lower estimate of the mean time on cetuximab plus irinotecan treatment: 4.4 months compared with 8.8 months. Merck Serono's derivation of its estimate is based on its imposition of an artificial maximum time on cetuximab plus irinotecan treatment. When we use Merck Serono's model and lift its cap on the time on treatment, the ICER increases from £44,000 to £67,000 per QALY.

Cost-effectiveness of panitumumab compared with best supportive care

The estimate of cost-effectiveness from the PenTAG de novo model is £150,000 per QALY gained, with no alternative estimate being offered by the manufacturer.

Conclusions

On balance we conclude that, used for third- and subsequent-line treatment relative to best supportive care, cetuximab plus best supportive care, cetuximab plus irinotecan plus best supportive care and panitumumab plus best supportive care are effective but not cost-effective if a decision threshold of £20,000 per QALY or £30,000 per QALY is used.

There is no additional evidence on the effectiveness and cost-effectiveness of cetuximab used in second-line treatment to that informing the guidance on second-line use provided by technology appraisal No. 118.

In common with the manufacturer, we were not able to estimate the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy second or subsequent line because of the absence of RCT evidence.

Suggested research priorities

- Given the lack of clinical data for patients with *KRAS* WT status receiving cetuximab plus irinotecan, it would be useful to conduct a RCT for these patients comparing cetuximab plus irinotecan with cetuximab plus best supportive care or panitumumab plus best supportive care. It would be helpful to collect health-related quality of life data in such a trial.
- There is a need to have data documenting the proportions of patients on the various pathways of disease once metastatic colorectal cancer has occurred to better inform the clinical costs and overall costs.
- We cannot model the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy because of the absence of relevant clinical evidence. Ideally a RCT should be conducted, but only if this was thought to be a potentially important use of the agent by the wider clinical community.
- Given that the mean duration of cetuximab plus irinotecan treatment strongly influences its cost-effectiveness, and that it is not known with certainty, further data on this parameter from the BOND RCT (Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.

N Eng J Med 2004;**351**:337–45) of cetuximab plus irinotecan compared with cetuximab would be helpful.

- Given that the medical management cost data come from a study of women with breast cancer from over 10 years ago, collecting data on the medical management of metastatic colorectal cancer would be useful.

Ongoing trials identified in the course of this appraisal indicate that some of the gaps in knowledge may already be being addressed.

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Editorial contact: nihredit@southampton.ac.uk

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Editorial contact: nihredit@southampton.ac.uk