

# **Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer**

**Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Care Excellence: HTA 14/65/01**

15 January 2014

## **1. Title of the project**

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation.

## **2. Name of TAR team and project 'lead'**

**TAR Team** Peninsula Technology Assessment Group (PenTAG), Evidence Synthesis and Modelling for Health Improvement (ESMI), University of Exeter Medical School

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## **3. Plain English Summary**

The aim of this project is to review the clinical effectiveness and cost effectiveness of cetuximab and panitumumab in a multiple technology appraisal. This will include a review of TA176 (cetuximab), and a part review of TA240 (panitumumab) for previously untreated metastatic colorectal cancer (mCRC). The medical benefit and risks associated with these treatments will be assessed and compared across the

treatments and against available standard drug treatments. The review will also assess whether these drugs are likely to be considered good value for money for the NHS.

## **4. Decision problem**

### **4.1. Objectives**

This assessment will address the question: “What is the clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer?”

### **4.2. Background**

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.

Colorectal cancer is the third most common cancer in the UK after breast and lung cancer: in 2012, there were 34,322 people new registrations of colorectal cancer and 12,900 deaths.<sup>1</sup> Occurrence of colorectal cancer is strongly related to age, with almost three-quarters of cases occurring in people aged 65 or over.<sup>1</sup> Colorectal cancer is the second most common cause of cancer death in the UK.<sup>1</sup> Around half of people diagnosed with colorectal cancer survive for at least 5 years after diagnosis.<sup>1</sup>

Treatment of mCRC may involve a combination of surgery, chemotherapy, radiotherapy, and supportive care.<sup>1</sup> When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered.<sup>1</sup> For people with metastases only in their livers, complete resection appears to offer the best chance of long-term survival, providing 5 year survival rates ranging from 25% to 44%. Chemotherapy is an option to prolong survival and/or to make the primary tumour or metastases suitable for resection. NICE clinical guideline 131 recommends chemotherapy options including fluorouracil and folinic acid in combination with oxaliplatin (FOLFOX), tegafur in combination with fluorouracil and folinic acid, capecitabine in combination with oxaliplatin (XELOX), and capecitabine alone.<sup>1</sup> In practice, fluorouracil and folinic acid may also be used in combination with irinotecan (FOLFIRI) in some people for whom oxaliplatin is not suitable.<sup>1</sup> Chemotherapy may be combined with biological agents such as cetuximab (recommended for people

satisfying criteria specified in technology appraisal 176),<sup>2</sup> panitumumab,<sup>3</sup> and bevacizumab (not recommended by NICE but funded via the Cancer Drugs Fund\*<sup>4</sup>).

The choice and effectiveness of some treatments for mCRC may be influenced by genetic markers.<sup>5</sup> Several studies in CRC have shown that, owing to the convergence of the epidermal growth factor receptor (eGFR) and Kirsten rat sarcoma (KRAS) pathways, patients with mutations in genes in the rat sarcoma (RAS) family (specifically KRAS and neuroblastoma rat sarcoma [NRAS]) treated with the eGFR specific antibodies cetuximab and panitumumab derive considerably less benefit than patients with wild type.<sup>6</sup> Approximately 50% of people with advanced colorectal cancer have mutations in the KRAS or NRAS genes.<sup>5</sup>

At the time of technology appraisal 176 (2009), RAS wild-type status was defined based on a single part ('exon') of the KRAS gene, and testing typically focused on KRAS codons 12 and 13.<sup>7</sup> However, subsequent evidence suggested that mutations in other KRAS codons and other genes downstream of EGFR may also confer drug resistance explaining why some individuals with KRAS codon 12 and 13 wild-type tumours did not respond to therapy.<sup>7</sup> The absence of mutations in the NRAS gene and in 2 further exons (3 and 4) of KRAS was found to improve the effectiveness of cetuximab and panitumumab.<sup>7</sup> These developments led the European Medicines Agency to update the marketing authorisations for cetuximab and panitumumab in 2013 by restricting the indication in colorectal cancer to the treatment of patients with RAS (i.e. both KRAS and NRAS) wild-type tumours.<sup>8;9</sup> It is this change to the licensed indications for these products that provides the rationale for this appraisal.<sup>5</sup>

### 4.3. Interventions

Cetuximab (Erbitux<sup>®</sup>, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR), inhibiting the growth of tumours expressing EGFR.<sup>10</sup> Cetuximab has a UK marketing authorisation for the treatment of patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer (mCRC), either in combination with FOLFOX (FOL [folinic acid]; F [Fluorouracil, 5-FU], OX [Oxaliplatin, Eloxatin]), or irinotecan-based chemotherapy.<sup>10</sup>

Panitumumab (Vectibix<sup>®</sup>, Amgen) is a recombinant, fully human immunoglobulin (Ig) G2 monoclonal antibody that binds to EGFR, blocking its signalling pathway and inhibiting the growth of tumours.<sup>11</sup> It has a UK marketing authorisation for use in combination with FOLFOX, for treating previously untreated, RAS wild-type mCRC.<sup>11</sup>

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\* Subject to availability of funding through the Cancer Drugs Fund

Panitumumab is also licensed for use second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan), although clinical trials have also measured the effectiveness of panitumumab in combination with FOLFIRI for previously untreated mCRC.<sup>11</sup>

#### **4.4. Place of the interventions in the treatment pathway**

##### **4.4.1. NICE TA176: Cetuximab for the first-line treatment of mCRC**

In the previous assessment (TA176):

- Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of mCRC only when all of the following criteria are met:
  - (1) the primary colorectal tumour has been resected or is potentially operable;
  - (2) the metastatic disease is confined to the liver and is unresectable;
  - (3) the patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab; and
  - (4) the manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.<sup>2</sup>
- Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of mCRC only when all of the following criteria are met:
  - (1) the primary colorectal tumour has been resected or is potentially operable;
  - (2) the metastatic disease is confined to the liver and is unresectable;
  - (3) the patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab; and
  - (4) the patient is unable to tolerate or has contraindications to oxaliplatin.<sup>2</sup>

Patients who meet the criteria above should receive treatment with cetuximab for no more than 16 weeks.<sup>2</sup> At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.<sup>2</sup>

#### 4.4.2. NICE TA240: Panitumumab for the first-line treatment of mCRC

The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE technology appraisal 240) was terminated because no evidence submission was received from the manufacturer or sponsor of the technology.<sup>3</sup> Therefore NICE was unable to make a recommendation about the use in the NHS of panitumumab in combination with chemotherapy for the treatment of mCRC.<sup>3</sup>

#### 4.5. Comparators

The interventions should be compared with each other, and with:

- FOLFOX
- XELOX
- FOLFIRI
- Capecitabine
- Tegafur, folinic acid and fluorouracil
- Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy (not recommended by NICE but funded via the Cancer Drugs Fund<sup>†</sup>).<sup>5</sup>

#### 4.6. Population and relevant subgroups

The population of interest to the current appraisal is people with previously untreated, *RAS* wild-type mCRC.<sup>5</sup> We note that the interventions are only licensed in adults (aged  $\geq 18$  years).<sup>10;11</sup>

If the evidence allows, the use of the interventions will be considered in subgroups based on the location of metastases (inside and/or outside the liver).<sup>5</sup>

##### 4.6.1. Outcomes

Evidence on the following outcomes will be considered:

- overall survival
- progression-free survival

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<sup>†</sup> Subject to availability of funding through the Cancer Drugs Fund

- response rate
- rate of resection of metastases
- adverse effects of treatment
- health-related quality of life (HRQoL).<sup>5</sup>

## **5. Methods for synthesis of evidence of clinical effectiveness**

This MTA will include a review of cetuximab and panitumumab for previously untreated mCRC.<sup>5</sup> It will include a review of TA176 and part review of TA240.<sup>2:3</sup> The systematic review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.<sup>12</sup>

### **5.1. Search strategy**

The search strategy for clinical effectiveness studies will include the following search methods:

- Searching of bibliographic and ongoing trials databases.
- Searching of conference proceedings.
- Contact with experts in the field.
- Scrutiny of bibliographies of retrieved papers and company submissions.

The following bibliographic and ongoing trials databases will be searched for clinical effectiveness studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library including the Cochrane Systematic Reviews Database, CENTRAL, DARE and HTA databases; Web of Science (Thomson Reuters); ClinicalTrials.gov; UK Clinical Research Network's (UKCRN) portfolio; ISRCTN registry; WHO International Clinical Trials Registry Platform (ICTRP).

The following websites will be searched for conference proceedings:

- National Cancer Research Institute <http://conference.ncri.org.uk/>
- American Association for Cancer Research <http://aacrmeetingabstracts.org/>
- American Society of Clinical Oncology <http://meetinglibrary.asco.org/abstracts>

In addition to the clinical effectiveness searches, the Health Management Information Consortium (HMIC, Ovid) will be searched for grey literature.

The database searches will be developed by an information specialist. Search filters will be used to limit the searches to randomised controlled trials (excluding Cochrane Library databases and HMIC), and all searches will be limited to English language studies where possible. No date limits will be used.

All bibliographic references retrieved by the searches will be exported to Endnote X7 and de-duplicated (using automatic and manual methods) before screening.

## 5.2. Study selection criteria and procedures

Studies retrieved from the searches will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in Table 1. First, abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by discussion, with involvement of a third reviewer when necessary. Full texts of identified studies will be obtained and screened in the same way. At each step studies which do not satisfy those criteria will be excluded; abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality.

**Table 1. Inclusion criteria**

	<b>Inclusion criteria</b>	<b>Notes</b>
<b>Population</b>	Adults with previously untreated, RAS wild-type mCRC	Interventions only licensed in adults
<b>Intervention</b>	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy Panitumumab, in combination with fluorouracil-containing regimens	NOTE: Panitumumab, in combination with FOLFIRI is licensed for use second-line. However, there are studies evaluating its effectiveness in previously untreated patients. Therefore, ensure that the trial population is relevant to the review
<b>Comparators</b>	The interventions should be compared with each other, and with: <ul style="list-style-type: none"> <li>• FOLFOX</li> <li>• XELOX</li> <li>• FOLFIRI</li> <li>• Capecitabine</li> <li>• Tegafur, folinic acid and</li> </ul>	

	fluorouracil • Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy (not recommended by NICE but funded via the Cancer Drugs Fund <sup>a</sup> )	
<b>Outcomes</b>	Overall survival Progression-free survival Response rate Rate of resection of metastases Adverse events HRQoL	
<b>Study design</b>	Randomised controlled trials	We will also identify systematic reviews (per definition specified in Section 5.2.1) of RCTs
<b>Key:</b> HRQoL = health-related quality of life; mCRC = metastatic colorectal cancer; RCTs = randomised controlled trials <b>Notes: (a)</b> Subject to availability of funding through the Cancer Drugs Fund		

### 5.2.1. Study design

The review of clinical effectiveness will include any RCT reporting at least one of the outcomes of interest. However, if any outcomes of interest are lacking RCT evidence or if the RCTs do not provide an adequate length of follow-up, we will extend our search and inclusion criteria to controlled clinical trials. Furthermore, these criteria would also be relaxed for consideration of adverse events, where non-randomised and observational studies may be included. However, scoping searches indicate sufficient RCT evidence should be available.

Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be included as sources of references for finding further RCTs and to compare with our systematic review.

For the purpose of this review, a systematic review will be defined as one that has:

- a focused research question
- explicit search criteria that are available to review, either in the document or on application
- explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest



- a critical appraisal of included studies, including consideration of internal and external validity of the research
- a synthesis of the included evidence, whether narrative or quantitative.

### **5.3. Data extraction strategy**

Included full papers will be split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

### **5.4. Quality assessment strategy**

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using criteria based on those proposed by the NHS Centre for Reviews and Dissemination for RCTs.<sup>12</sup> The potential generalisability of the study will also be assessed, as well as the judged applicability to the current organisation, clinical pathways and practices of the NHS in England.

### **5.5. Methods of analysis/synthesis**

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary.

If appropriate (i.e., if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses. We are aware that there are different definitions of RAS WT (Section 4.2) which we will consider when pooling data.

Where appropriate, meta-analysis will be carried out using STATA and/or WinBugs software, with the use of fixed- and/or random-effects appropriate to the assembled datasets. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical

terms, by the  $\chi^2$  test for homogeneity and the  $I^2$  statistic. If data allows, a network meta-analysis will be considered.

## **5.6. Publication bias**

We will investigate the likelihood of publication bias using funnel plots if there are sufficient included studies.

Reporting bias<sup>‡</sup> in our systematic review and meta-analyses will be assessed according to the Cochrane Handbook for Reviewers.<sup>13</sup>

In addition, the reported outcomes and methods of analysis in included RCTs will be compared with those described in the registered protocols of those trials, and any discrepancies or uncertainties noted. Where there are potentially includable trials in trial registries for which no reported reports or papers are found, these will be documented and efforts made to find out whether the trial was conducted, completed, and whether the findings are available. Conversely, where a reported RCT is not recorded in a trial registry, this will be clearly noted.

## **6. Methods for synthesising evidence of cost-effectiveness**

The aims of the review of economic studies are to:

- gain insights into the key drivers of cost-effectiveness in this disease area.
- get an overview of the alternative modelling approaches that have been adopted in this disease and treatment area.
- provide a summary of the findings of previous relevant cost-utility, cost-effectiveness, and cost-benefit studies generalisable to the UK.

### **6.1. Review of economic studies**

#### **6.1.1. Search strategy**

The search strategy for economic studies will include the following search methods:

- Searching of bibliographic and ongoing trials databases.
- Searching of conference proceedings.
- Scrutiny of bibliographies of retrieved papers and company submissions.

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<sup>‡</sup> Where the term 'reporting bias' covers all types of publication, language, outcome, location etc biases defined in the Cochrane Handbook.

The following databases will be searched for economic studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); NHS EED (via Cochrane Library); EconLit (EBSCO); Web of Science (Thomson Reuters).

A supplementary search for health utilities will be run in the following databases: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); PsycINFO (Ovid); Web of Science (Thomson Reuters); SchARR Health Utilities Database.

The searches will be developed by an information specialist. Search filters will be used to limit the searches to economic or health utilities studies as appropriate, and searches will be limited to English language studies where possible. No date limits will be used. All references retrieved by the searches will be exported to Endnote X7 and de-duplicated (using automatic and manual methods) before screening.

Relevant studies identified and included in the company's submissions will also be included.

#### **6.1.2. Inclusion and exclusion criteria**

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness Section 5.2, page 7, except:

- Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequences analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)
- Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS.

Study selection will be based on the above inclusion/exclusion criteria.

### **6.1.3. Quality assessment**

The quality of identified cost–utility analyses will be assessed using the checklist developed by Evers and colleagues (2005)<sup>14</sup> by one reviewer. Where studies are based on decision models they will be further quality assessed using the checklist developed by Philips and colleagues (2004; 2006).<sup>15;16</sup>

### **6.1.4. Synthesis**

Economic studies will be summarised and synthesised using tabulated data and narrative synthesis.

## **6.2. Economic modelling**

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and PSS using a decision analytic model. The aims of the economic modelling are to:

- estimate the base case lifetime incremental QALYs and incremental costs of the defined comparators according to NICE reference case methods (or with only limited deviations from NICE reference case methods due to deficiencies in available data), and assess the cost-effectiveness of the various interventions in the NHS.
- describe and explore the impact of structural and parameter uncertainty on the estimates of cost-effectiveness .
- enable comparison of the cost-utility estimates between the company's economic analyses and those by us, the assessment group.

The evaluation will be constrained by available evidence. The evaluation will produce estimates of incremental cost per QALY gained, unless there is insufficient evidence to estimate utility/HRQoL.

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. If required parameters are not available from good quality published studies in the relevant patient group, we

may use data from sponsor submissions to NICE or from other unpublished data, or where no clinical data is available, from expert opinion.

Resource use (including RAS mutation testing) will be specified and valued from the perspective of the NHS and PSS. The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, sponsor submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost databases for the most recent year, or, where these are not relevant, extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

ICERs estimated from company models will be compared with the respective ICERs from our model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

### **6.2.1. Methods for measuring and valuing health effects**

Ideally, health-related quality of life (HRQOL) should be reported directly from patients. The value of changes in patients' HRQOL (that is, utilities) should be based on public preferences using a choice-based method.<sup>17</sup> The EQ-5D will be the preferred measure of HRQOL for the purposes of estimating QALYs.<sup>17</sup> In the absence of reliable EQ-5D utility data from relevant trials or patient groups, the use of alternative sources for utility weights for health states will be informed by the NICE Guide to the methods of technology appraisal (2013).<sup>17</sup>

### **6.2.2. Time horizon, perspective and discounting**

The time horizon of our analysis will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.<sup>17</sup>

## 7. Handling of information from the companies

All data submitted by the companies will be considered if received by NICE no later than 17:00 on 27th April 2015. Data arriving after this date may not be considered.

The industry submissions will be:

- Critically appraised for integrity and quality of evidence
- Used as a source of data, to identify studies not located by the searches and that meet the review inclusion criteria.
- Used to compare any submitted industry model(s) with our independent economic assessment.

Any economic evaluations included in the company submission will be assessed against NICE's guidance on the Methods of Technology Appraisal<sup>17</sup> and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where we have undertaken further analyses, using models submitted by the companies or via *de novo* modelling and cost effectiveness analysis, a comparison will be made of the alternative models.

Tabulated summaries and technical commentaries on the economic models used in the company submissions will be provided. This will not be a full critique as for a single technology appraisal but will be used to reflect on the results from the PenTAG *de novo* model and to discuss any differences.

Any 'commercial in confidence' data provided by companies, and specified as such, will be highlighted in blue and underlined in our assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by companies, and specified as such, will be highlighted in yellow and underlined in our assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

## 8. Expertise in this TAR team

Name	Institution	Expertise
<b>Mary Bond</b>	PenTAG, ESMI, University of Exeter Medical School	Project management, systematic review
<b>Simon Briscoe</b>	PenTAG, ESMI, University of Exeter Medical School	Information specialist

<b>Helen Coelho</b>	PenTAG, ESMI, University of Exeter Medical School	Systematic review
<b>Louise Crathorne</b>	PenTAG, ESMI, University of Exeter Medical School	Project management, systematic review and economic evaluation
<b>Martin Hoyle</b>	PenTAG, ESMI, University of Exeter Medical School	Economic modelling, economic evaluation, and Guarantor of the final report
<b>Nicola Huxley</b>	PenTAG, ESMI, University of Exeter Medical School	Project management; economic modelling and economic evaluation
<b>Chris Hyde</b>	PenTAG, ESMI, University of Exeter Medical School	Systematic review and economic evaluation
<b>Mark Napier</b>	Royal Devon and Exeter Hospital, Devon	Consultant oncologist
<b>Key:</b> ESMI = Evidence Synthesis and Modelling for Health Improvement; PenTAG = Peninsula Technology Assessment Group		

**Other external experts:** We will also work in collaboration with other external advisors *[[to be advised pre final protocol]]*.

**Other PenTAG resources:** Depending on the agreed scope of work we will draw on other researchers from PenTAG as required.

## 9. TAR centre

The Peninsula Technology Assessment Group is part of the Evidence Synthesis and Modelling for Health Improvement (ESMI) group at the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Health technology assessment projects include:

- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85): a systematic review and economic model (in progress)
- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in children (review of technology appraisal guidance 99): a systematic review and economic model (in progress)

- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model (2014)
- Bosutinib for previously-treated chronic myeloid leukaemia: a single technology appraisal (2013)
- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model
- The psychological consequences of false positive mammograms: a systematic review
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a critique of the submission from Novartis
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer
- The clinical- and cost effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model
- Machine perfusion systems and cold static storage of kidneys from deceased donors.
- The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults
- The harmful health effects of recreational Ecstasy: A systematic review of observational evidence
- Assessment of surrogate outcomes in model-based cost effectiveness analyses within UK health technology reports: a methodological review
- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over.



- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years.
- The effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: a systematic review and economic model.
- The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease: a systematic review and economic model
- The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation.
- Surveillance of cirrhosis for the development of hepatocellular carcinoma: systematic review and economic analysis.
- Surveillance of Barrett's oesophagus: exploring the uncertainty.
- The cost effectiveness of testing for hepatitis C in former injecting drug users.
- Do the findings of case series vary systematically by methodological characteristics.
- The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
- Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
- Systematic review of endoscopic Sinus Surgery for Nasal Polyps.
- Screening for hepatitis C in GUM clinic attenders and injecting drug users.
- The effectiveness and cost effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

## **10. Competing interests of authors**

None

**11. Timetable/milestones**

<b>Action</b>	<b>Expected due date</b>
Draft protocol due	29 December 2014
Final protocol due	19 January 2015
Company submissions due to NICE	27 April 2015
Progress report due	13 May 2015
Draft assessment report due to NICE	17 July 2015
Assessment report due	7 August 2015
1 <sup>st</sup> Appraisal Committee meeting	15 October 2015
2 <sup>nd</sup> Appraisal Committee meeting	6 January 2016

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## Appendix A: MEDLINE search strategies

### Clinical effectiveness

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to November Week 3 2014

Date searched: 02/12/2014

Searcher: Simon

Hits: 446

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or "ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin\*).tw.
5. (CRC or mCRC).tw
6. exp Colorectal Neoplasms/
7. colon/
8. rectum/
9. or/4-8
10. (random\* or rct\* or "controlled trial\*" or "clinical trial\*").tw.
11. randomized controlled trial.pt.
12. 10 or 11
13. 3 and 9 and 12
14. limit 13 to english language

### Cost effectiveness (economics and model)

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to November Week 3 2014

Date searched: 02/12/2014

Searcher: Simon

Hits: 124

Lines 1-9 same as clinical effectiveness search strategy -

10. (pharmacoeconomic\* or economic\* or price\* or pricing\* or cost\* or cba or cea or cua or "health utilit\*" or "value for money").tw.
11. (fiscal or funding or financial or finance\* or expenditure\* or budget\*).tw.
12. ("resource\* alloca\*" or "resource\* use").tw.
13. exp Economics/
14. exp models, economic/
15. exp "Costs and Cost Analysis"/
16. Cost of illness/
17. ec.fs.
18. (decision adj2 (model\* or tree\* or analy\*)).tw.
19. markov.tw.
20. decision trees/
21. or/10-20
22. 3 and 9 and 21
23. limit 22 to english language

**Utilities (economics and model)**

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to November Week 3 2014

Date searched: 02/12/2014

Searcher: Simon

Hits: 71

Lines 1-9 same as clinical effectiveness search strategy -

10. ("quality of life" or QoL or HRQL or HRQoL or AqoL).tw.
11. quality of life/
12. ("quality adjusted life year\*" or QALY\*).tw.
13. quality-adjusted life years/
14. ("quality of wellbeing" or QWB).tw.
15. ("health\* year\* equivalent\*" or HYE\*).tw.
16. "health status".tw.
17. health status/
18. health status indicators/
19. ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six").tw.
20. ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty").tw.
21. ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen").tw.
22. ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12" or "SF twelve").tw.
23. ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten").tw.
24. ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six").tw.
25. (Euroqol or "EQ-5D").tw.
26. Health Surveys/
27. questionnaire\*.tw.
28. exp Questionnaires/
29. "willingness to pay".tw.
30. ("time trade off" or "time tradeoff" or tto).tw.
31. ("visual analog\* scale" or VAS).tw.
32. (health adj2 (utilit\*3 or value\* or preference\*)).tw.
33. ("health utilities index\*" or (hui or hui1 or hui2 or hui3 or hui4 or hui-1 or hui-2 or hui-3 or hui-4)).tw.
34. disutil\*.tw.
35. "standard gamble".tw.
36. "discrete choice".tw.
37. or/10-36
38. 3 and 9 and 37
39. limit 38 to english language