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The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

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Plain English Summary

Around 30,000 people in England and Wales are diagnosed with colorectal cancer (bowel cancer) each year. The treatment for colorectal cancer depends mainly on the location of the tumour in the colon or rectum and the stage of the disease. The mainstay of treatment for colorectal cancer is surgical removal of the tumour, although surgery may offer limited benefit for people with metastatic disease (people whose disease has spread to other organs). Most patients with metastatic disease receive chemotherapy (drugs which kill cancer cells), whereby substances travel through the bloodstream, reaching and affecting cancer cells all over the body. A range of alternative chemotherapies are available for the treatment of colorectal cancer.

This review will assess the effectiveness and cost-effectiveness of two new chemotherapies for metastatic colorectal cancer. Bevacizumab (also called Avastin) is used in combination with intravenous 5-fluorouracil/folinic acid (5-FU/FA) or intravenous 5-FU/FA plus irinotecan, and is indicated for the first-line treatment of patients with metastatic carcinoma of the colon or rectum. Cetuximab (also called Erbitux) is used in combination with irinotecan, and is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy. EGFR is stimulated by growth factors that normally help to regulate the growth of many different cells in the body, but can also stimulate cancer cells to grow. Many cancer cells actually require growth factors that bind to EGFR for their survival.

The review will focus on the differences in overall survival, progression-free survival, health-related quality of life benefits, tumour response rates, time to treatment failure,

side effects and toxicity resulting from the use of bevacizumab and cetuximab compared to current standard chemotherapies used to treat patients with metastatic colorectal cancer. The costs and cost-effectiveness of bevacizumab and cetuximab will be assessed from the perspective of the NHS and Personal Social Services.

Evidence on the effectiveness of bevacizumab and cetuximab will be obtained by systematically reviewing and appraising relevant randomised controlled trials (RCTs). In the event that no RCTs are available, evidence from non-randomised studies will be reviewed. Evidence on the cost-effectiveness of bevacizumab and cetuximab will be obtained by systematically reviewing existing economic evaluations of these drugs compared to conventional treatments. It is anticipated that an economic evaluation will also be undertaken by the Assessment Group to determine whether bevacizumab and cetuximab represent good value for money for the NHS.

1. Decision problem

1.1 Purpose of the assessment

The assessment will address the question *"What is the clinical and cost-effectiveness of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer?"* The clinical and cost-effectiveness of bevacizumab (Avastin) in combination with 5-FU/FA or irinotecan plus 5-FU/FA will be assessed in comparison to an established fluorouracil-containing or releasing regimen. The clinical and cost-effectiveness of cetuximab (Erbitux) in combination with irinotecan will be assessed in comparison to oxaliplatin in combination with infusional 5-FU/FA, or active/best supportive care alone.

Whilst the clinical and cost-effectiveness of bevacizumab and cetuximab will be assessed within a single report, these are not competing therapies and are indicated for different lines of treatment and different patient populations. Therefore, bevacizumab and cetuximab will not be compared with each other, instead the review will focus on differences between these therapies and their current relevant comparators in terms of overall survival, progression-free survival, tumour response rates, time to treatment failure, adverse events and toxicity, as well as any significant impacts that such treatments may have on health-related quality of life (HRQoL).

1.2 Clear definition of the interventions

Two interventions will be assessed within the review in accordance with their licensed indications. These are:

(1) First-line therapy using bevacizumab in combination with 5-FU/FA or with 5-FU/FA plus irinotecan
(2) Second- or subsequent-line therapy using cetuximab in combination with irinotecan

1.3 Place of the intervention in the treatment pathway

Bevacizumab in combination with intravenous 5-FU/FA or intravenous 5-FU/FA plus irinotecan is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Cetuximab in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy. The review will not consider the use of these therapies in an adjuvant setting.

1.4 Relevant comparators
The relevant comparators for bevacizumab are established fluorouracil-containing or releasing regimens given as first-line therapy. The relevant comparators for cetuximab are oxaliplatin in combination with infusional 5-FU/FA, or active/best supportive care alone (that is without chemotherapy) given as second-line or subsequent therapy.

1.5 Population and relevant subgroups
The relevant population for the assessment of bevacizumab is people with untreated metastatic colorectal cancer. The relevant population for the assessment of cetuximab is people with EGFR-expressing metastatic colorectal cancer who have previously failed irinotecan-including therapy. Subject to the availability of evidence, the review will seek to define subgroups of patients that may be suited to treatment with bevacizumab or cetuximab; this will depend not only on disease status but also on a patient's own overall functional status.

1.6 Key factors to be addressed
The objectives of the review are:
1. to evaluate the relative clinical effectiveness of bevacizumab and cetuximab in terms of progression-free survival, overall survival, tumour response rates, time to treatment failure and health-related quality of life compared with current standard treatments;
2. to evaluate the side-effect profiles of bevacizumab and cetuximab;
3. to estimate the incremental cost-effectiveness of bevacizumab and cetuximab compared with current standard therapies;
4. to estimate the overall cost to the NHS in England and Wales.

The review will also discuss any available evidence relating to the relative effectiveness of different modalities for the delivery of 5-FU, e.g. bolus versus infusional regimens.

2. Report methods for synthesis of evidence of clinical effectiveness

2.1 Search strategy
The search will aim to identify all studies relating to bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Search strategies will include the terms bevacizumab and cetuximab. The following databases will be searched: Medline, Embase, CINAHL, BIOSIS, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Controlled Trials Register (CCTR), the Science Citation Index and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA) and OHE HEED. Pre-Medline will also be searched to identify any studies not yet indexed on Medline. Current research will be identified through searching the National Research Register (NRR), the Current Controlled Trials register and the MRC Clinical Trials Register. Any industry submissions, as well as any relevant systematic reviews will also be hand-searched in order to identify any further clinical trials. Searches will not be restricted by language, date or publication type. The MEDLINE search strategy is presented in Appendix 1.

2.2 Types of studies included
The assessment will include the following study types:

- systematic reviews
- randomised controlled trials (RCT)
- non-randomised studies
- economic evaluations.

2.3 Inclusion and exclusion criteria
2.3.1 Inclusion criteria for bevacizumab
Subjects: patients with untreated metastatic colorectal cancer
Intervention: bevacizumab in combination with 5-FU/FA or with irinotecan plus 5-FU/FA
Comparators: Established fluorouracil-containing or -releasing regimens
Outcome measures:
- overall survival
- progression-free survival
- tumour response rates
- time to treatment failure
- adverse events\ toxicity
- health-related quality of life

2.3.2 Inclusion criteria for cetuximab
Subjects: patients with EGFR-expressing metastatic colorectal cancer who have previously failed irinotecan-including therapy
Intervention: cetuximab in combination with irinotecan
Comparators: oxaliplatin in combination with infusional 5-FU/FA, or active/best supportive care alone
Outcome measures:
- overall survival
- progression-free survival
- tumour response rates
- time to treatment failure
- adverse events\ toxicity
- health-related quality of life

2.3.3 Exclusion criteria
Reviews of primary studies will not be included in the analysis, but will be retained for discussion. Studies which are considered methodologically unsound will be excluded from the review.

2.4 Data extraction strategy
Data will be extracted by one researcher, and checked by a second, using a standardised data extraction form (see Appendix 2); any disagreements will be resolved by discussion.

2.5 Quality assessment strategy
Published papers will be assessed according to the accepted hierarchy of evidence, whereby meta-analyses of RCTs are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative. The quality of randomised controlled trials will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination (see Appendix 3). The

purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analysis.

Use of data from non-randomised studies will be considered if there is insufficient evidence from good-quality RCTs. These will be assessed using the CASP checklist for non-randomised studies.

The quality of economic literature will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond et al (Methods for the Economic Evaluation of Health Care Programmes, Oxford University Press, Oxford). The Drummond checklist is presented is Appendix 3.

2.6 Methods of analysis/synthesis

Pre-specified outcomes as described in section 2.3 will be tabulated and discussed within a descriptive synthesis. Where statistical synthesis is appropriate, the Assessment Team will use summary statistics extracted from the published literature and the methodology described by Parmar and colleagues (Parmar MKB, Torri VB, Stewart L, 1998, Statist. Med. 17, 2815-2834). Where sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials (especially those with inadequate concealment of the allocation schedule) affects the results. A mathematical model will be developed to synthesise the available data on survival, progression-free survival and health-related quality of life of patients receiving bevacizumab or cetuximab or current standard therapies. All survival and progression-free survival durations will be expressed in terms of both the mean and median.

2.7 Methods for estimating quality of life

Ideally, evidence on the impact of these therapies on HRQoL will be available directly from the trials included within the review. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources.

3. Report methods for synthesising evidence of cost-effectiveness

3.1 Identifying and systematically reviewing published cost-effectiveness studies

The review of guidance #33 "The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer" included a critical appraisal of existing studies which have estimated the costs and benefits of irinotecan, oxaliplatin and 5-FU/FA. Additional studies relating to the costs and effects associated with bevacizumab and cetuximab will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 2.1; this economic search filter is presented in Appendix 1. Studies included within the cost-effectiveness review will be critically appraised using the Drummond checklist.

3.2 Methods for estimating costs and cost-effectiveness

The review of guidance #33 "The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer" reported the development of a mathematical model to estimate the cost per progression-free life year gained, the cost per life year gained and the cost per QALY gained for first- and second-line irinotecan, 5-FU/FA, and oxaliplatin, as well sequences and combinations of these chemotherapies. The model extrapolated Kaplan-Meier survival curves from recent clinical trials to

estimate the mean duration of survival and progression-free survival, and estimated the costs of such benefits using resource use data collected within recent trials. It is anticipated that the cost-effectiveness and cost-utility of bevacizumab and cetuximab will be estimated using this existing model framework. It should be noted however, that a paucity of evidence on the clinical effectiveness of cetuximab is anticipated; the modelling of cetuximab is thus dependent on the availability of suitable clinical effectiveness evidence and resource use data.

Sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments. Multivariate Monte Carlo methods will be undertaken to generate information on the likelihood that each treatment is optimal. The results of this probabilistic sensitivity analysis will be presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

4. Handling the company submission(s)

Any 'commercial in confidence' data taken from the company submission will be clearly highlighted in the assessment report. The industry dossier will be used as a source of data for studies that meet the inclusion criteria for both the clinical and cost-effectiveness review. Any clinical and cost effectiveness information contained in the company submission to NICE, and not otherwise available in published reports, will be reviewed using the same criteria as used for other sources of evidence. It is envisaged that the industry models will be analysed in detail with respect to their strengths, weaknesses and assumptions. These will be compared to the model constructed by ScHARR.

5. Timescales for the assessment

Milestone	Deadline
Draft protocol	17th May 2005
Final protocol	31st May 2005
Progress report	6th September 2005
Draft Assessment Report	25th January 2006
Assessment report	22nd February 2006

Competing interests of authors
None

Appendix 1 MEDLINE search strategy for clinical effectiveness

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Database: Ovid MEDLINE(R) <1966 to April Week 2 2005>
Search Strategy:
--------------------------------------------------------------------------------
1     (bevacizumab or avastin).af. (177)
2     216974-75-3.rn. (0)
3     Recombinant humanised monoclonal antibody to VEGF.af. (0)
4     (cetuximab or erbitux).af. (246)
5     or/1-4 (380)
6     exp Colorectal Neoplasms/ (82082)
7     NEOPLASMS/ (139140)
8     CARCINOMA/ (44988)
9     ADENOCARCINOMA/ (84122)
10     or/7-9 (260268)
11     Colonic Diseases/ (10019)
12     Rectal Diseases/ (4997)
13     exp COLON/ (36936)
14     exp RECTUM/ (25629)
15     or/11-14 (68404)
16     10 and 15 (3097)
17     (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (19771)
18     (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (1435)
19     (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (2109)
20     (adenocarcinoma adj3 (colorectal or colon$ or rect$ or
intestin$ or bowel)).tw. (6911)
21     (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (47335)
22     (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (14668)
23     (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (3728)
24     (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (4260)
25     or/17-24 (78583)
26     6 or 16 or 25 (105981)
27     randomized controlled trial.pt. (198570)
28     controlled clinical trial.pt. (67854)
29     Randomized Controlled Trials/ (36257)
30     Random Allocation/ (52720)
31     Double-Blind Method/ (80748)
32     Single-Blind Method/ (8758)
33     or/27-32 (337506)
34     clinical trial.pt. (400686)
35     exp Clinical Trials/ (162978)
36     (clin$ adj25 trial$).ti,ab. (107454)
37     ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or
mask$)).ti,ab. (79972)
38     PLACEBOS/ (23504)
39     placebos.ti,ab. (1088)
40     random.ti,ab. (78029)
41     Research Design/ (40035)
42     or/34-41 (638420)
43     33 or 42 (667083)
44     5 and 26 and 43 (100)
45     from 44 keep 1-100 (100)
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MEDLINE search strategy for cost-effectiveness

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Database: Ovid MEDLINE(R) <1966 to April Week 3 2005>
Search Strategy:
--------------------------------------------------------------------------------
1     (bevacizumab or avastin).af. (181)
2     216974-75-3.rn. (0)
3     Recombinant humanised monoclonal antibody to VEGF.af. (0)
4     (cetuximab or erbitux).af. (251)
5     or/1-4 (387)
6     exp Colorectal Neoplasms/ (82207)
7     NEOPLASMS/ (139290)
8     CARCINOMA/ (45030)
9     ADENOCARCINOMA/ (84214)
10     or/7-9 (260550)
11     Colonic Diseases/ (10026)
12     Rectal Diseases/ (5000)
13     exp COLON/ (36978)
14     exp RECTUM/ (25647)
15     or/11-14 (68464)
16     10 and 15 (3099)
17     (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (19791)
18     (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (1436)
19     (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (2110)
20     (adenocarcinoma adj3 (colorectal or colon$ or rect$ or
intestin$ or bowel)).tw. (6923)
21     (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (47428)
22     (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (14692)
23     (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (3731)
24     (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or
bowel)).tw. (4268)
25     or/17-24 (78715)
26     6 or 16 or 25 (106150)
27     ECONOMICS/ (23805)
28     exp "Costs and Cost Analysis"/ (114641)
29     "Value of Life"/ (4410)
30     exp Economics, Hospital/ (13268)
31     exp Economics, Medical/ (9610)
32     Economics, Nursing/ (3638)
33     Economics, Pharmaceutical/ (1449)
34     exp Models, Economic/ (4122)
35     exp "Fees and Charges"/ (21396)
36     exp BUDGETS/ (8711)
37     ec.fs. (196197)
38     (Costs or cost or costed or costly or costing$).tw. (144451)
39     (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
(72193)
40     Quality-Adjusted Life Years/ (2111)
41     economic burden.tw. (969)
42     "Cost of Illness"/ (6769)
43     exp quality of life/ (45694)
44     Quality of Life.tw. (45697)
45     life quality.tw. (1451)
46     hql.tw. (55)
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47     (Sf36 or sf36 or sf thirtysix or sf thirty six or short form
36 or short term thirty six or short form thirtysix or shortform
36).tw. (1717)
48     Qol.tw. (4497)
49     (Euroqol or eq5d or eq 5d).tw. (578)
50     Qaly$.tw. (1109)
51     Quality adjusted life year$.tw. (1342)
52     Hye$.tw. (343)
53     Health$ year$ equivalent$.tw. (30)
54     Health utilit$.tw. (279)
55     HUI.tw. (249)
56     Quality of wellbeing$.tw. (2)
57     Qwb.tw. (94)
58     Quality of well being.tw. (506)
59     (Qald$ or qale$ or qtime$).tw. (34)
60     or/27-59 (441793)
61     5 and 26 and 60 (17)
62     from 61 keep 1-10 (10)
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Appendix 2 Randomised controlled trials data extraction form

(based on NHS CRD Report No. 4. {NHS Centre for reviews and Dissemination. *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York; 2001.}

STUDY & DESIGN	DATA EXTRACTION	
Trial	REVIEW DETAILS	
	Author, year	
Study design	**Objective**	
	Publication type (ie full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	INTERVENTIONS	
	Focus of interventions (comparisons)	
	Description	
	T1: Intervention group, dose, timings	
	T2: Control group, dose, timings	
	Intervention site (health care setting, country)	
	Duration of intervention	
	Length of follow up	
	STUDY CHARACTERISTICS	
	Method of randomisation	
	Description	
	Generation of allocation sequences	

	Allocation concealment?	
	Blinding level	
	Numbers included in the study	
	Numbers randomised	T1: T2:
	POPULATION CHARACTERISTICS	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean yr.)	
	Gender (male/female)	
	Performance scale/status	
	Tumor stage	
	Other information	
	Were intervention and control groups comparable?	
	OUTCOMES	
	Definition of primary outcomes	
	Definition of secondary outcomes	
	Definition of tertiary outcomes	
	Definition of other outcomes	

	ANALYSIS	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	
	Was attrition adequately dealt with?	
	Number (%) followed-up from each condition	
	Compliance with study treatment	
	Adherence to study treatment	
	RESULTS	
	Quantitative (e.g. estimates of effect size); qualitative results; effect of the intervention on other mediating variables *(Example Outcomes: overall survival, relapse-free survival, disease free survival, response rates etc)*	
	Overall survival	
	Progression-free survival	
	Toxicity/adverse effects	
	Time to treatment failure	
	Quality of life	
	Tumour response rate	
	Cost information	

	Other information	
	SUMMARY	
	Authors' overall conclusions	
	Reviewers comments	

Appendix 3 Randomised controlled trial quality assessment scale

(based on NHS CRD Report No. 4. {NHS Centre for reviews and Dissemination. *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York; 2001.}

	Yes/No
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were the eligibility criteria for study entry specified?	
Were any co-interventions identified that may influence the outcomes for each group?	
Were the outcome assessors blinded to the treatment allocations?	
Were the individuals who administered the intervention blinded to the treatment allocation?	
Were the participants who received the intervention blinded to the treatment allocation?	
Was the success of the blinding procedure assessed?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were the reasons for withdrawal stated?	
Was an intention-to-treat analysis included?	

Y – item addressed; N – no; ? – not enough information or not clear; NA –not applicable

The Drummond checklist for assessing quality of economic literature

1. Was a well-defined question posed in answerable form?
    1.1 Did the study examine both costs and effects of the service(s) or programme(s)?
    1.2 Did the study involve a comparison of alternatives?
    1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often?
    2.1 Were any important alternatives omitted?
    2.2 Was (Should) a do-nothing alternative (be) considered?

3. Was the effectiveness of the programmes or services established?
    3.1 Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
    3.2 Was effectiveness established through an overview of clinical studies?
    3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. Were all the important and relevant costs and consequences for each alternative identified?
    4.1 Was the range wide enough for the research question at hand?
    4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
    4.3 Were capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)?
    5.1 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
    5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?
    6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements).
    6.2 Were market values employed for changes involving resources gained or depleted?
    6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?

6.4 Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility been selected)?

7. Were costs and consequences adjusted for differential timing?
   7.1 Were costs and consequences which occur in the future 'discounted' to their present value?
   7.2 Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?
   8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?
   9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed?
   9.2 If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?
   9.3 Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10 Did the presentation and discussion of study results include all issues of concern to users?
   10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
   10.2 Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?
   10.3 Did the study discuss the generaliseability of the results to other settings and patient/client groups?
   10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?
10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?