
# NCCHTA

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# Taxanes for the adjuvant treatment of early breast cancer

## TAR team

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield.

## Lead

Ward, Sue, Ms.
Senior Operational Research Analyst,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA.
Direct line: 0114 222 0816
Fax: 0114 272 0785
E-mail: s.e.ward@sheffield.ac.uk

**Plain English Summary**

Around 37,000 women in England and Wales are diagnosed with breast cancer each year. The treatment for breast cancer depends mainly on the stage of the disease.

Around 80% of women (around 30,000 in England and Wales) present with early disease. The mainstay of treatment for early stage cancer is surgical removal of the tumour. Adjuvant therapy with chemotherapy agents may be indicated, based on their age and prognosis. For instance, women are more likely to receive chemotherapy if the the primary cancer in the breast is large, or if the lymph nodes contain breast cancer cells. The aim of adjuvant therapy is to kill off any cancer cells that have broken away from the tumour in the breast and spread before it was removed. It therefore reduces the risk of the cancer coming back.

This review will assess the effectiveness and cost-effectiveness of taxanes (docetaxel and paclitaxel) for the adjuvant treatment of early breast cancer. Taxanes are chemotherapy drugs which may be included as part of a chemotherapy regimen, alone or in combination with anthracycline. In some instances, the taxane may be substituted for one or more drugs generally administered in the regimen.

Docetaxel and paclitaxel prevent the growth of cancer cells by affecting cell structures called microtubules, which play an important role in cell functions. In normal cell growth, microtubules are formed when a cell starts dividing. Once the cell stops dividing, the microtubules are broken down or destroyed. Taxanes stop the microtubules from breaking down; cancer cells become so clogged with microtubules that they cannot grow and divide. The goal of taxane therapy in breast cancer is to stop cancerous cells from dividing, thereby preventing the growth and spread of cancer.

Docetaxel (Taxotere, Sanofi Aventis) has a UK marketing authorisation for the adjuvant treatment of patients with operable breast cancer and positive axillary lymph nodes, in combination with doxorubicin and cyclophosphamide. Docetaxel is currently also licensed in the UK for the treatment of other stages of breast cancer and for non-small cell lung cancer.

Paclitaxel has a UK marketing authorisation for the adjuvant treatment of patients with operable and node-positive breast cancer following anthracycline and cyclophosphamide therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended anthracycline and cyclophosphamide therapy. It is manufactured in the UK as Taxol (Bristol-Myers Squibb). Generic paclitaxel is also manufactured by Mayne Pharma and by Teva. Paclitaxel is currently also licensed in the UK for the treatment of other forms of cancer, including other stages of breast cancer, and specific types of ovarian cancer, small-cell lung cancer and AIDS-related Kaposi's sarcoma.

The review will focus on the differences in overall survival, disease-free survival, health-related quality of life benefits, local and distant recurrence, adverse events and toxicity resulting from the use of docetaxel and paclitaxel compared with the current anthracycline-based chemotherapy used to treat patients with early breast cancer. The costs and cost-effectiveness of docetaxel and paclitaxel will be assessed from the perspective of the NHS and Personal Social Services.

Evidence on the effectiveness of docetaxel and paclitaxel 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 docetaxel and paclitaxel will be obtained by systematically reviewing existing economic evaluations of these drugs compared with anthracycline based chemotherapy. An economic evaluation will also be undertaken by the Assessment Group to determine whether docetaxel and paclitaxel represent good value for money for the NHS.

## 1. Decision problem

### *1.1 Purpose of the decision to be made*

The assessment report will address the following question, in order to assist the production of guidance to NHS commissioners in England and Wales:

*"Are docetaxel and paclitaxel clinically and cost effective compared with non-taxane containing chemotherapy regimens including anthracycline agent, for the adjuvant treatment of women with early stage breast cancer?"*

### *1.2 Clear definition of the intervention*

The taxanes are a class of anti-cancer drugs, originally derived the Pacific Yew tree. Both drugs have a similar mechanism of action. The goal of taxane therapy in breast cancer is to prevent cell division, resulting in cell death.

Docetaxel (Taxotere, Sanofi Aventis) has a UK marketing authorisation for the adjuvant treatment of patients with operable breast cancer and positive axillary lymph nodes**, in combination with** doxorubicin and cyclophosphamide. Docetaxel is currently also licensed in the UK for the treatment of other stages of breast cancer and for non-small cell lung cancer.

Paclitaxel has a UK marketing authorisation for the adjuvant treatment of patients with operable and node-positive breast cancer **following** anthracycline and cyclophosphamide therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended anthracycline and cyclophosphamide therapy. It is manufactured in the UK as Taxol (Bristol-Myers Squibb Pharmaceuticals Ltd, Hounslow, UK). Generic paclitaxel is also manufactured by Mayne Pharma and by Teva. Paclitaxel is currently also licensed in the UK for the treatment of other forms of cancer, including other stages of breast cancer, and specific types of ovarian cancer, small-cell lung cancer and AIDS-related Kaposi's sarcoma.

Both docetaxel and paclitaxel are administered by intravenous infusion.

### *1.3 Place of the intervention in the treatment pathway(s)*

Taxanes are indicated for the adjuvant treatment of women with early breast cancer, eligible to receive anthracycline-based chemotherapy; that is to say, they are administered following surgical resection in combination with or following anthracycline-based chemotherapy.

### *1.4 Relevant comparators*

NICE currently recommends that adjuvant chemotherapy for early breast cancer should consist of 4 to 8 cycles of a combination of drugs, including an anthracycline [epirubicin or doxorubicin (adriamycin)]. Some of the commonest regimens in current use include: AC (doxorubicin and cyclophosphamide), FEC (epirubicin, cyclophosphamide and fluorouracil), and epi-CMF (epirubicin followed by cyclophosphamide, methotrexate and fluorouracil)

Comparison of taxanes will be made with chemotherapy regimens including anthracycline agents. Currently docetaxel has UK marketing authorisation for treatment in combination with doxorubicin and cyclophosphamide and paclitaxel has a UK marketing authorisation for treatment following anthracycline and cyclophosphamide. The two mains comparisons will be :

1. Sequential taxane therapy (taxane following anthracycline therapy) versus anthracycline-based non-taxane therapy

   Relevant trials include : NSABP-28 and CALGB9344 - both trials compare 4 cycles of AC (doxorubicin and cyclophosphamide) followed by 4 cycles of **paclitaxel** with 4 cycles of AC (doxorubicin and cyclophosphamide).

2. Combination taxane therapy versus anthracycline-based non-taxane therapy

   Relevant trials include: BCIRG001 –this trial compares 6 cycles of TAC (doxorubicin and cyclophosphamide and **docetaxel**) with 6 cycles of FAC (doxorubicin and cyclophosphamide and fluorouracil)

At the request of NICE, the review team will also review the clinical effectiveness of trials which use taxanes in regimens which fall outside their current marketing authorisation and therefore the scope. Examples include MDACC (4 cycles of paclitaxel followed by 4 cycles of FAC compared with 8 cycles of FAC) and US Oncology 9735 (4 cycles of AC compared with 4 cycles of docetaxel and cyclophosphamide). This informal augmentation of the remit currently extends only to variations from the licensed interventions and **not**, currently, to populations which fall outside the current scope (for instance, women scheduled for neo-adjuvant chemotherapy).

### *1.5 Population and relevant sub-groups*

Women with early stage (stages I or II or stage IIIa of the American Joint Committee on Cancer (AJCC) system)) breast cancer.

See Appendix 1 for definition of stages.

Relevant subgroups include: age, nodal status; expression of molecular markers, HER2 positive or negative (oestrogen receptor positive versus negative, progesterone receptor positive versus negative), prognostic status (however evaluated – Nottingham Prognostic Index, St Gallens criteria, etc). These will be considered where evidence is available.

### *1.6 Key factors to be addressed*

The objectives of the review are:

1 to evaluate the relative clinical effectiveness of docetaxel and paclitaxel in terms of overall survival, disease-free survival and health-related quality of life compared with the current treatment with an anthracycline-based chemotherapy
2 to evaluate the side-effect profiles of docetaxel and paclitaxel;
3 to estimate the incremental cost-effectiveness of docetaxel and paclitaxel compared with current standard therapies;
4 to estimate the overall cost to the NHS in England and Wales.

If the evidence allows, chemotherapy regimens containing docetaxel and paclitaxel may also be compared to each other.

## Report methods for synthesis of evidence of clinical effectiveness

### *2.1 Search strategy*

The search will aim to identify all studies relating to taxanes for the treatment of early stage breast cancer. 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, the MRC Clinical Trials Register and the proceedings of the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). 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 2.

### *2.2 Types of studies included*

The assessment will include the following study types:

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

Where evidence from RCTs is absent for an indication, observational studies will be included. 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.

### *2.3 Inclusion criteria*

*Participants:* Women who have had surgery for early stage breast cancer (Stages I and II and IIIa of the AJCC system)

*Interventions:* either docetaxel or paclitaxel as part of a chemotherapy regimen, alone or in combination with anthracycline, (including instances where the taxane is substituted for one or more drugs generally administered in the regimen), administered adjuvant to surgical resection. Endocrine therapy may be used if its administration is consistent between groups.

*Comparator:* The same underlying chemotherapy regimen, accepting safety-based dose modification.

*Outcomes:*

- Overall survival (primary outcome)
- Disease-free survival
- Local and distant recurrence

- Adverse events \ toxicity
- Health-related quality-of-life

*2.4 Exclusion criteria*

*Participants:* Men; women with advanced stage breast cancer; women receiving neo-adjuvant chemotherapy.

*Interventions:* Taxanes administered in the adjuvant setting where the comparator is not the same underlying chemotherapy as in the chemotherapy arm; **taxanes administered as neoadjuvant chemotherapy**.

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

*2.5 Sub-groups to be examined*

Where data is available the following subgroups will be analysed separately: age, nodal status; expression of molecular markers, HER2 positive or negative (oestrogen receptor positive versus negative, progesterone receptor positive versus negative), prognostic status (however evaluated – Nottingham Prognostic Index, St Gallens criteria, etc).

*2.6 Data extraction strategy*

Data will be extracted by one researcher, and checked by a second, using a standardised data extraction form (see Appendix 3); any disagreements will be resolved by discussion.

*2.7 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 4). 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 Critical Appraisal Skills Programme (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 and colleagues (*Methods for the Economic Evaluation of Health Care Programmes*, Oxford University Press, Oxford). The Drummond checklist is presented is Appendix 5.

*2.8 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, disease-free survival, and health-related quality of life of patients receiving taxanes or not. The model will consider the use of taxanes within current licensed indications only.

The impact of using docetaxel and paclitaxel as therapy for early breast cancer on the potential use and effectiveness of these drugs in advanced breast cancer will be considered where evidence allows.

*2.9 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. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model.

## 3. Report methods for synthesising evidence of cost-effectiveness

*3.1 Identifying and systematically reviewing published cost-effectiveness studies*

Studies relating to the costs and effects associated with taxanes and anthracycline-based chemotherapy 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 2. Studies included within the cost-effectiveness review will be critically appraised using the Drummond checklist.

*3.2 Methods for estimating costs and cost-effectiveness*

A mathematical model will be developed to estimate the cost per life-year gained and the cost per QALY gained (assuming that suitable quality of life data is identified) for taxanes. The model will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from a variety of published sources. It should be noted however, that modelling is dependent on the availability of suitable clinical effectiveness evidence and resource use data.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how secure the results of the economic analyses are, given the available evidence. In addition, uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA), where uncertainty of all input variables is modelled with probability distribution of their value. The information derived from PSA will be summarised graphically using cost effectiveness acceptability curves.

## 4. Handling the company submission(s)

Any 'commercial in confidence' data taken from the company submission will be clearly highlighted and underlined 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. Industry models will be analysed in detail with respect to their strengths, weaknesses and assumptions. The models will be compared with the model constructed by ScHARR, and where large differences between pivotal results exist, the discrepancies will be analysed

## Competing interests of authors

None known.

**Appendix 1: Definitions of cancer stages**

*Stage I - invasive breast cancer in which the tumour measures up to two centimetres, and no lymph nodes are involved.*

*Stage IIA: No tumour is found in the breast but it is in 1 to 3 axillary lymph nodes, or the tumour is less than 2 cm and has spread to 1 to 3 axillary lymph nodes or found by sentinel node biopsy as microscopic disease in internal mammary nodes but not on imaging studies or by clinical exam, or the tumour is larger than 2 cm in diameter and less than 5 cm but hasn't spread to axillary nodes. The cancer hasn't spread to distant sites.*
*Stage IIB: T2, N1, M0/ T3, N0, M0: The tumour is larger than 2 cm in diameter and less than 5 cm and has spread to 1 to 3 axillary lymph nodes or the tumour is larger than 5 cm and does not grow into the chest wall and has not spread to lymph nodes. The cancer hasn't spread to distant sites.*

*Stage IIIA* **-** *The tumour is smaller than 5 cm in diameter and has spread to 4 to 9 axillary lymph nodes, or the tumour is larger than 5 cm and has spread to 1 to 9 axillary nodes or to internal mammary nodes. The cancer hasn't spread to distant sites.*

**Appendix 2 Search strategies**

MEDLINE search strategy for clinical effectiveness

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1 taxol.tw.
2 taxotere.tw.
3 anzatax.tw.
4 114977-28-5.rn.
5 33069-62-4.rn.
6 docetaxel.mp. (
7 paclitaxel.mp. or exp PACLITAXEL/
8 Taxoids/
9 taxane$.tw.
10 or/1-9
11 [exp *Breast Neoplasms/]
12 ((breast$ or mamma$) adj5 (cancer$ or carcin$ or tumor$ or tumour$ or neoplasm$)).tw.
13 11 or 12
14 10 and 13
15 limit 14 to clinical trial
16 [from 15 keep 1-739]
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 Randomized Controlled Trials/
20 random allocation/
21 double blind method/
22 Single-Blind Method/
23 17 or 18 or 19 or 20 or 21 or 22
24 clinical trial.pt.
25 [exp clinical trials/]
26 PLACEBOS/
27 placebo$.ti,ab.
28 random$.ti,ab.
29 research design/
30 (clin$ adj25 trial$).ti,ab.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
32 or/24-31
33 (animals not human).sh.
34 23 not 33
35 32 not 33
36 35 or 34
37 Comparative Study/
38 [exp Evaluation Studies/]
39 Follow-Up Studies/
40 Prospective Studies/
41 (control$ or prospectiv$ or volunteer$).ti,ab.
42 or/37-41
43 42 not 33
44 43 not (34 or 36)
45 34 or 36 or 44
46 14 and 45

MEDLINE search strategy for cost-effectiveness

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**Appendix 3 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:<br>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? | |
| | 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 | |
| | Disease-free survival | |
| | Local recurrence | |
| | Distant recurrence | |
| | Toxicity/adverse effects | |
| | Health-related quality of life | |
| | Cost information | |
| | Other information | |
| | Summary | |
| | Authors' overall conclusions | |
| | Reviewers comments | |

**Appendix 4 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

**Appendix 5 : 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?