Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

8th September 2008

1. Title of the project:

Topotecan for the second-line treatment of small cell lung cancer

2. Plain English Summary

Lung cancer is one of the leading causes of cancer death in the UK. Lung cancers are divided into two main groups based on the type and size of the tumour cells – small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC accounts for approximately one in five of all cases of lung cancers and is largely caused by cigarette smoking. It is an aggressive form of cancer that grows quickly and spreads to other areas of the body rapidly, forming secondary tumours known as metastases. SCLC is classified into two stages, limited-stage and extensive-stage, according to the level of progression of the disease. In limited-stage disease, cancer is found in one lung, the tissues between the lungs and nearby lymph nodes only. In extensive-stage disease, the cancer has spread beyond the lung to other parts of the body.

For most patients with SCLC, the prognosis is poor and current treatments do not cure the cancer. Surgery is an option, but is only suitable for a small minority of patients where the cancer is confined to one lung. Patients with SCLC usually have widespread disease at the time of diagnosis and thus first-line treatment involves chemotherapy, often in conjunction with radiotherapy. Although response rates to first-line treatment are generally high (particularly for limited-stage disease), many patients relapse and the cancer usually recurs within a year. Patients who respond to initial chemotherapy but experience relapse, or whose disease progressed during primary therapy, have a poor prognosis and short life expectancy – two to three months if untreated and rarely more than six months even after second-line chemotherapy treatment.

Second-line therapy may be re-treatment with the first-line therapy, or an alternative therapy. This review will summarise the results of clinical trials which evaluate the use of topotecan for second-line treatment of patients with SCLC. The report will include an economic evaluation to give an indication of the cost-effectiveness of topotecan for the NHS in England and Wales.

3. Decision problem

The aim of this health technology assessment is to assess the clinical effectiveness and cost-effectiveness of topotecan for the second-line treatment of small cell lung cancer. NICE clinical guidelines on the diagnosis and treatment of lung cancer (NSCLC and SCLC) were published in

2005,[1] but these guidelines do not include topotecan as this was licensed more recently in January 2006. Topotecan has been evaluated in a peer-reviewed systematic review of chemotherapy for SCLC[2] with search dates up to October 2005. This health technology assessment will provide an up to date systematic review for topotecan used within its licensed indications for patients with SCLC.

3.1 Background

Lung cancer

There are two main types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC are usually centrally located with extensive mediastinal involvement and tend to grow rapidly and spread quickly to distant sites (metastases).[3] SCLC is typically classified using a two-stage system, limited-stage disease and extensive-stage disease (see below for further details) according to the level of progression of the disease. Limited-stage disease is generally confined disease, and extensive-stage disease refers to cases where there is also metastatic spread.[1] Most SCLCs present with metastases - a recent review found that two thirds of patients have extensive disease on presentation.[4]

In most patients the disease is symptomatic on presentation. In some, these are non-specific symptoms such as fatigue, anorexia, and weight loss, whilst in others there are more direct signs and symptoms such as breathlessness, chest discomfort and haemoptysis (blood stained sputum).[3] SCLC is also associated with systemic symptoms related to paraneoplastic syndromes.[5] These are caused by the release of bioactive substances produced by the tumour or in response to the tumour[3] and include endocrine syndromes and neurologic syndromes.[5] The most common endocrine syndrome in SCLC is inappropriate secretion of antidiuretic hormone (leading to water retention), hyponatraemia (low sodium), hypotension (low blood pressure) and Cushing's syndrome. Digital clubbing and hypertrophic pulmonary osteoarthropathy are common skeletal manifestations.[3]

SCLC is initially very sensitive to chemotherapy, with 60% to 90% of patients with limited-stage disease responding to first-line therapy and 40% to 70% of patients achieving a complete response (CR).[2] For extensive-stage disease, approximately 50-85% respond to first-line therapy.[6]

Epidemiology

Lung cancer is one of the most common cancers in England, accounting for some 15% of all malignancies in males and 11% in females in 2005.[7] In Europe and the UK, lung cancer was the most common cause of death from cancer in 2006.[8] Cancer statistics do not appear to distinguish between the different histological types of lung cancer in their rates. However, estimates suggest that small cell lung cancers account for approximately 10-20% of lung cancers.[1,9] Therefore crude estimates of the epidemiology of SCLC can be generated from the overall rates of lung cancer.

There were 33,181 new cases of lung cancer in England and Wales in 2005[7,10] with more cases in males than in females (19,261 males, 13,920 females). European age-standardised incidence rates of lung cancer in England in 2005 were 72.9 per 100,000 in males and 50.6 per 100,000 in females.[7] The corresponding rates in Wales in 2005 were 62.5 per 100,000 (males) and 39.5 per 100,000 (females).[10] In 2006, estimates of the age-standardised incidence rates of lung cancer in the UK were lower than estimates for all European Union countries for males (57.1 per 100,000 compared to 71.8 per 100,000) but higher for females (34.6 per 100,000 versus 21.7 per 100,000).[8] Taking a range of 10-20% for SCLC, an estimate of the number of new cases of SCLC per year (using 2005 estimates for England and Wales[7,10]) would be in the region of 3,300 – 6,600.

The incidence of lung cancer rises with increasing age. Very few people are diagnosed under the age of 40 years, and the incidence shows a peak in rates around ages 75-84 years. Most cases occur in people over the age of 60 years.[11] Time trends in the incidence of lung cancer show a decline in rates in males between 1995 and 2004 but over the same time period there has been almost no change in the rates in females.[11] Overall though, rates have decreased. The proportion of lung cancer cases of small cell type has been steadily falling over the years and reasons for this are unclear, but it has been attributed to changing smoking habits.[12-14]

Prognosis

The survival rate of patients with lung cancer has improved in recent years,[15] although deaths from lung cancer remain high (5-year age-standardised survival rate of 5.8% and 6.4% in males and females respectively in 1996-1999) in the UK.[15] SCLCs tend to grow rapidly and have a greater tendency to widely metastasise.[16] Without treatment, SCLC has an aggressive clinical course, with life expectancy of about 3.5 months for limited-stage disease and six weeks for extensive-stage disease. With treatment, median survival for patients with limited-stage disease is 16 to 22 months; for those with extensive-stage disease median survival is 10 months.[17] Approximately 20%–40% of patients with limited-stage SCLC and fewer than 5% of patients with extensive-stage SCLC survive 2 years.

Aetiology

Risk factors include tobacco exposure, gender, diet and chronic lung disease. Smoking is the leading cause of lung cancer, accounting for approximately 80-90% of cases.[13,18] When compared to never smokers, those who have smoked without quitting successfully have a 20-fold increase in lung cancer risk.[19] The risk for lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day.[19]

Diagnosis and Staging

Lung cancer is usually suspected on the basis of an initial clinical assessment – taking into account the patients' symptoms, history, physical examination – in addition to an abnormal chest x-ray. Confirmation of the diagnosis is then achieved using histological and cytological tests. Selection of the most appropriate treatment is determined primarily by the stage of disease. As previously mentioned, SCLC presents as limited-stage disease or extensive-stage disease, classified according to the level of progression of disease. Limited-stage SCLC is defined as disease that is confined to one hemi-thorax and its regional lymph nodes, in the absence of malignant effusion, and which can be encompassed in one radiotherapy port. Nearly one third of SCLC patients present with limited disease.[9,20] Extensive-stage disease is disease beyond the confines of the thorax at diagnosis, with the presence of systemic metastases, and that cannot be encompassed safely in one radiotherapy port. The prognosis for patients with extensive-stage disease is much poorer than for those with limited-stage disease.

Current treatment options

Recommendations for first-line therapy for SCLC, from the NICE guideline,[1] are that patients should be offered a multi-drug platinum-based chemotherapy. Those with limited-stage disease should be offered radiation concurrently with the first or second cycle, or following completion if a good partial response is seen within the thorax. Prophylactic cranial irradiation is also recommended in those with limited-stage disease and complete or good partial response. In those with extensive-stage disease, radiation should be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial response in the thorax. Second-line chemotherapy is recommended to be offered at relapse if the disease responded to first-line therapy.

The platinum-based treatment combinations for first-line therapy that are offered (and recommended by NICE) are either cisplatin or carboplatin with etoposide. In some instances anthracycline-based drug combinations (cyclophosphamide / doxorubicin [adriamycin] / vincristine (CAV) or / doxorubicin / cyclophosphamide / etoposide (ACE)) are given. Other drugs may include: paclitaxel, methotrexate, irinotecan, usually in combinations.

Second-line therapy is offered if a good response is achieved by the first-line treatment.[1] Evidence suggests that the best results from second-line therapy are achieved in those with at least three months between response and progression.[21] Tumour response to first-line therapy can be categorised as either sensitive, resistant, or refractory.[2] Sensitive refers to a tumour response of more than 90 days, resistant to tumour recurrence within 90 days and refractory to tumours that either never responded or progressed during first-line therapy. It is generally thought that those with a sensitive response will have the greatest potential for second line therapy.[2] Second-line therapy may be re-treatment with the

first-line therapy, or an alternative therapy if re-treatment with the first-line therapy is contraindicated, and is discussed on an individual basis.

3.2 Definition of the intervention

Topotecan (Hycamtin®) is a cytotoxic anti-cancer agent. Its mechanism of action is to inhibit the nuclear enzyme topoisomerase I, an enzyme involved in DNA replication. This leads to double-strand breaks when the DNA is replicated and eventually results in cell death. Intravenous topotecan for SCLC was licensed in January 2006; oral topotecan was licensed more recently in March 2008. Topotecan is also licensed for use in patients with ovarian cancer. The recommended dose of topotecan for SCLC is 1.5mg/m^2 body surface area/day administered by intravenous infusion over 30 minutes daily for five days, with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression. One pharmaceutical company has UK marketing authorisation.

3.3 Place of the intervention in the treatment pathway

The current NICE lung cancer clinical guidelines[1] recommend that all patients with newly diagnosed SCLC should be offered four to six cycles of a multi-drug platinum-based chemotherapy regimen (see above). Second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy. Supportive and palliative care is given concurrently. Topotecan is proposed as a second-line treatment for SCLC. It is indicated as monotherapy for patients with relapsed SCLC for whom re-treatment with the first-line chemotherapy regimen is not considered appropriate.

3.4 Population and relevant sub-groups

The population for this review is as described above. Potential subgroups can be described according to the presence of any liver metastases, cardiovascular contraindications to anthracycline use, or by time to relapse. Comment on the effectiveness of topotecan for any of these subgroups will be limited by the available data and the appropriateness of subgroup analyses (defined a priori, evidence that is statistically powered) within any identified trials.

4. Report methods for synthesis of evidence of clinical- and cost-effectiveness

A review of the evidence for clinical-effectiveness and cost-effectiveness will be undertaken systematically following the general principles outlined in CRD Report Number 4 (2nd Edition) 'Undertaking Systematic Reviews of Research on Effectiveness'.[22]

4.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (i) clinical effectiveness studies reporting on comparisons between topotecan (oral or IV, but not combined) and BSC or other chemotherapy regimens (as described in section 5.2); (ii) studies reporting on the cost-effectiveness of topotecan and different second-line treatments, and the relative comparisons. The search strategy will also identify studies reporting resource use and costs, epidemiology and natural history.

The following electronic databases will be searched: The Cochrane library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); PreMedline In-Process & Other Non-Indexed Citations; Web of Knowledge Science Citation Index (SCI); Web of Knowledge ISI Proceedings; PsychInfo; Biosis; UKCRN Study Portfolio and Current Controlled Trials. Key cancer resources (such as the American Society of Clinical Oncology (ASCO), European CanCer Organisation (ECCO) etc.) and relevant cancer symposia will also be searched. The draft search strategy for Medline is shown in Appendix 11.1. This will be adapted for other databases.

Bibliographies of related papers will be assessed for relevant studies where possible. The manufacturers' submissions to NICE will be assessed for any additional studies which meet the inclusion criteria. Experts will be contacted to identify additional published and unpublished evidence.

Searches will be carried out from 1990 and will be limited to the English language. For the cost-effectiveness section, searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6.2) and may include a wider range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report.

4.2 Inclusion and exclusion criteria

4.2.1 Population

- Adults (≥18 years) with relapsed SCLC who responded to first-line treatment and for whom re-treatment with first-line therapy is not considered appropriate (due to contraindications, adverse effects).
- Patients may have limited stage disease or extensive stage disease.

- Response to initial treatment may be either complete response (CR) or partial response (PR).
- Patients who did not respond to first-line therapy (including patients whose tumours did not respond, or who progressed, during first-line treatment) will not be included.
- Studies with a mix of untreated and previously treated patients (or responders and non-responders), will not be included unless the groups are reported separately.

4.2.2 Intervention

- Intravenous topotecan
- Oral topotecan

(administered as second-line treatment)

- Studies with a focus on first-line treatment will not be included
- Effectiveness data for oral and intravenous topotecan will not be combined.

4.2.3 Comparators

- Intravenous and oral topotecan will be compared with each other
- Best supportive care (including radiotherapy)
- CAV (cyclophosphamide, doxorubicin, vincristine)
- Other chemotherapy regimens

4.2.4 Outcomes

Studies reporting one or more of the following outcomes will be included:

- time to disease progression
- progression-free survival
- response rate
- response duration
- overall survival
- symptom control
- health-related quality of life (using a validated measure)
- cost-effectiveness (incremental cost per life year gained) or cost-utility (incremental cost per quality adjusted life year gained)

Adverse effects of treatments will be reported if available within trials that meet the other inclusion criteria.

4.2.5 Types of studies

- Fully published randomised controlled trials (RCTs) will be included. If no RCTs are found, controlled clinical trials and prospective cohort studies (with a concurrent control) will be eligible for inclusion
- 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 results to be undertaken
- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations (cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses)
- Systematic reviews will be used as a source of references
- Case series, case studies, narrative reviews, editorials and opinions will not be included
- Non-English language studies will be excluded

4.3 Screening and data extraction process

4.3.1 Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed by two reviewers. Full papers of studies which appear potentially relevant will be requested for further assessment. These will be screened by two reviewers and a final decision regarding inclusion will be agreed. At each stage, any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

4.3.2 Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 11.2). Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

4.4 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD (University of York) criteria.[22] Economic evaluations will be assessed using criteria recommended by Drummond and colleagues[23] (see Appendix 11.1.3), and/or the format recommended and applied in the CRD NHS Economic Evaluation Database (using principles outlined in the NHS EED Handbook[24]). For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues[25]). Published studies carried out from the UK NHS and PSS perspective will be examined in more detail.

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus, and if necessary a third reviewer will be consulted.

4.5 Methods of data analysis/synthesis of clinical effectiveness data

Clinical effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using Review Manager (RevMan) software.

5. Methods of data analysis/synthesis of cost effectiveness data

5.1 Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations. Any economic evaluation included in sponsor submissions to NICE will be assessed using the same quality criteria as for published economic evaluations, but will be reported separately.

5.2 Economic Modelling

Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one using best available evidence. The perspective will be that of the NHS and Personal Social Services. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per Quality Adjusted Life Year (QALY) gained, as well as the cost per life year gained if data permit. Both cost and outcomes will be discounted at 3.5%.

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

- The biological disease process (i.e. knowledge of the natural history of the disease);
- The main diagnostic and care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest); and
- The disease states or events which are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

For patients receiving topotecan, or comparator treatments, for relapsed SCLC following first-line treatment, time to disease progression will be a major factor in defining costs of second-line treatment and is also likely to be a significant determinant of quality of life. Any improvements in overall survival or impacts on quality of life that may be associated with changes in progression-free survival

will need to be offset by consideration of the toxicity profile of alternative therapies. There is likely to be considerable uncertainty surrounding modes of treatment following disease progression on second-line treatment, which may have an influence on costs and quality of life. Clinical guidance will be sought to define appropriate protocols for patient management following disease progression on second-line treatment.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where 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 experts' clinical opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

The simulated population will be defined on the basis of both the published evidence about the characteristics of UK population with SCLC relevant to the licensed indication for topotecan, and the populations for which good quality clinical effectiveness is available. The base case results will be presented for the population of UK patients undergoing second-line treatment of SCLC. The time horizon for our analysis will initially be governed by follow-up data available from included clinical trials - we will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

5.2.1 Methods for estimating quality of life

The primary aim of treatment for SCLC is to palliate symptoms, prolong survival and maintain a good quality of life (QOL) with minimal adverse events from treatment. This assessment will aim to identify adverse effects of treatment that are likely to have a substantial impact on patients' quality of life, and to include these in estimates of health state utility while on treatment. Where presented, QOL information as well as incidence of adverse events and side effects of treatment will be extracted from included RCTs. Where QOL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. Ideally utility values will be taken from studies that have been based on "public" (as opposed to patient or clinician) preferences elicited using a choice-based method (in accordance with NICE methodological guidance).[26]

5.2.2 Analysis of uncertainty

Analysis of uncertainty will focus on cost-utility, assuming the 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 both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

6. Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the TAR team no later than 12/12/08. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's guidance on presentation,[26] will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Methods adopted, and incremental cost effectiveness ratios (ICERs) estimated from consultee models will be compared with published economic evaluations of topotecan included in the assessment report and with the results from the Assessment Group's analysis. Reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'academic in confidence' data or 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report.

7. Competing interests of authors

There are no competing interests.

8. References

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9. Appendices

9.1. Draft search strategy (Medline)

1 *Topotecan/
2 topotecan.ti.
3 hycamtin.ti,ab.
4 or/1-3
5 *Carcinoma, Small Cell/
6 (small cell$ adj3 (cancer$ or carcinoma$)).ti,ab.
7 (lung$ adj3 (cancer$ or carcinoma$ or neoplasm$ or tumor$ or tumour$)).ti,ab.
8 or/5-7
9 4 and 8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 clinical trial.pt.
13 exp clinical trials/
14 placebos/
15 random allocation/
16 double-blind method/
17 single-blind method/
18 cross-over studies/
19 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.
20 (random$ adj2 allocat$).tw.
21 placebo$.tw.
22 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
23 (crossover$ or (cross adj over$)).tw.
24 or/10-23
25 animals/
26 humans/
27 25 not (25 and 26)
28 24 not 27
29 9 and 28

9.2. Draft data extraction form

Reviewers:			
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Ref ID: Author: Year: Country: Study design: Number of centres: Funding:	<u>Group A:</u> n = Drug 1 Dose: Duration: Drug 2 Dose: Duration: <u>Group B:</u> n = Drug 1 Dose: Duration: Drug 2 Dose: Duration: Other interventions used:	Number of Participants: total and number per treatment group Sample attrition/dropout: total and number per treatment group Sample crossovers: Inclusion/exclusion criteria for study entry: Characteristics of participants: Gender (M/F), n (%): Age (yrs), mean (SD): Disease stage, n (%): Limited: Extensive: Performance status, n (%): 0: 1: 2: Max lesion diameter (cm), n (%): <2: 2 - <5: 5 - 10: >10: Previous treatment: Response, n (%): Partial: Complete: Duration of response to 1st-line chemotherapy, weeks: Liver metastases, n (%): Present: Absent:	Primary outcomes: Secondary outcomes: Methods of assessing outcomes: Length of follow-up:

RESULTS

Outcomes	**Treatment X (n=)**	**Comparator Y (n=)**	**P Value, 95% CI**
Overall survival			
Time to progression			
Progression-free survival			
Response rate			
Response duration			
Others			
HRQoL			
Adverse Effects			

Comments:

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Reviewers:

Methodological comments

- Allocation to treatment groups:
- Blinding:
- Comparability of treatment groups:
- Method of data analysis:
- Sample size/power calculation:
- Attrition/drop-out:

General comments

- Generalisability:
- Outcome measures:
- Inter-centre variability:
- Conflict of interests:

Quality criteria for assessment of RCTs

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

(see Quality criteria CRD 4.doc)

9.*3 Drummond et al check-list for assessing economic evaluations*

(**Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford. Oxford University Press. 2005**)

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 there any important alternatives omitted?
2.2. Was (should) a do-nothing alternative be considered?
3. Was the effectiveness of the programme 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 the 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 the cost 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 clinic 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 that occur in the future 'discounted' to their present values?
7.2. Was there 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 and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?
9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?
9.3. Were the 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 generalisability 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 relevant 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?