LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 PROJECT TITLE

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)

2 TAR TEAM AND 'LEAD'

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3 PLAIN ENGLISH SUMMARY

Lung cancer is the most common cancer in the world and the second most diagnosed in the UK after breast cancer. The most common type of lung cancer is non-small cell lung cancer. The majority of cases of lung cancer are diagnosed at a late stage when curative treatment is not available. The aims of treatment for late stage lung cancer are to prolong survival and improve quality of life. Chemotherapy may be offered to those considered suitable for this treatment. Initial (first-line) chemotherapy options will depend on the specific type of non-small cell cancer. Further (second-line) treatment may be offered to patients when their tumour begins to increase in size after first-line chemotherapy. The aim of this review is to assess the clinical and cost effectiveness of two second-line treatments for non-small cell lung cancer, erlotinib and gefitinib when compared with each other, docetaxel and best supportive care. Evidence for clinical effectiveness will be derived from a systematic review of randomised controlled trials. The key outcomes to be considered are overall survival, progression-free survival, tumour response rate, adverse effects of treatment and health-related quality of life. The evidence for cost effectiveness will be derived from clinical trial evidence as well as published economic evaluations, modelling studies and other data sources. Cost effectiveness will be expressed in terms of incremental cost per quality adjusted life years. Costs will be considered from an NHS and Personal Social Services perspective.

4 DECISION PROBLEM

4.1 Clarification of the research question and scope

The remit of this review is to appraise the clinical and cost effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of NSCLC following prior chemotherapy (review of NICE technology appraisals 162[1] and 175[2]).

4.2 Background

Lung cancer is the most common cancer in the world and the second most diagnosed in the UK after breast cancer. In 2011, 34,000 people were diagnosed with lung cancer in England and Wales[3] and there were 30,000 deaths from lung cancer.[4] The majority (68%) of cases of lung cancer occur in people over the age of 60 years.[5] Prognosis is poor as two thirds of people are diagnosed at a late stage (stage IIIB or IV) when curative treatment is not possible.[6]

The most common type of lung cancer is non-small cell lung cancer (NSCLC) accounting for approximately 78% of lung cancers in the UK.[7] Non-small cell lung cancers are further differentiated into three main histological subgroups, squamous cell carcinoma (33%), adenocarcinoma (25%) and large cell carcinoma (4%). Approximately 36% of patients are listed as being NSCLC 'not-otherwise specified' (NOS), 1% are carcinoma in situ and 1% are bronchioloalveolar.[8] The relative proportions of these subgroups vary over time, by population and by stage of disease.

For patients presenting with NSCLC stage IIIB, the 5-year survival rate is around 7 to 9%; for patients presenting with NSCLC stage IV, the 5-year survival rate varies from 2 to 13%.[9] Patients with NSCLC can be further differentiated as having either epidermal growth factor receptor (EGFR) activating mutation positive (M+) or negative (M-) status. Approximately 10% of patients in UK clinical practice will be of EGFR M+ status.[10]

For the majority of patients with stage IIIB or stage IV disease, the aims of treatment will be to prolong survival and improve quality of life. Chemotherapy should be offered to patients considered suitable (usually indicated by a WHO performance status [PS] of 0 or 1 or a Karnofsky score of 80 to 100). The presenting tumour histology together with PS, ease of administration and patient preference will determine the most appropriate type of treatment for patients with NSCLC.

4.2.1 First-line treatment options

There are a number of first-line chemotherapy treatment options recommended by the National Institute for Health and Clinical Excellence (NICE). These include platinum-based (cisplatin or carboplatin) doublet chemotherapy with docetaxel, gemcitabine, paclitaxel or vinorelbine (CG121[8]). Pemetrexed (Alimta®) plus cisplatin is an option for patients with non-squamous NSCLC (TA181[11]). Single agents gefitinib (Iressa®) or erlotinib (Tarceva®) are options for patients with locally advanced or metastatic EGFR M+ NSCLC (TA192[12] and TA258[13]).

4.2.2 Maintenance treatment options

Maintenance treatment has recently become an option for a limited group of patients. Pemetrexed as a single agent maintenance treatment is an option for patients with locally advanced or metastatic non-squamous disease whose disease has not progressed following first-line chemotherapy treatment with a platinum-based doublet containing gemcitabine, paclitaxel or docetaxel (TA190[14]).

4.2.3 Second-line treatment options

Current NICE recommendations for second-line treatment of NSCLC include docetaxel monotherapy (CG121[8]) or erlotinib monotherapy (TA162[15]). Docetaxel is an anti-mitotic treatment administered intravenously. It is licensed as a second-line treatment for patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy.

Erlotinib is an orally administered epidermal growth factor tyrokinase inhibitor (EGFR TKI). It is licensed for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Erlotinib is only recommended as an alternative to docetaxel if it is provided at an overall treatment cost equal to that of docetaxel.[15] Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom

docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.[15]

Gefitinib is also an orally administered EGFR TKI. It is licensed for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK i.e. patients who are EGFR M+. NICE was unable to recommend the use of gefitinib as a second-line treatment option for patients in England and Wales as the single technology appraisal process (2009) was terminated due to the manufacturer's failure to provide an evidence submission.[2]

Pemetrexed is an antifolate agent. It is licensed as a monotherapy for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) after prior chemotherapy. NICE did not recommend pemetrexed as a second-line treatment for locally advanced or metastatic NSCLC (TA124).[16]

In clinical practice, it is unlikely that patients would be re-treated with the same therapy they received at first-line.

4.3   The present appraisal

The present appraisal will be conducted in-line with the decision problem set out by NICE in the final scope.[9] This is replicated in Table 1. The interventions to be considered are erlotinib and gefitinib and the relevant patient population is adults with locally advanced or metastatic NSCLC. The interventions will be compared with each other and with docetaxel and best supportive care. The outcome measures to be considered include survival (overall and progression-free), response rates, adverse effects of treatment and health-related quality of life. Subgroups to be considered (if evidence allows) will be those based on histology and EGFR mutation status. The cost-effectiveness evidence will be expressed in quality adjusted life years (QALYs). The time horizon will be sufficiently long to reflect any differences in costs or outcomes between technologies. Mutational testing and patient access schemes will also be taken into account in the analyses.

4.3.1 Implications of the scope

The Assessment Group (AG) notes that gefitinib is only licensed for patients with EGFR M+ status; this means that patients who are EGFR M- are not eligible for treatment with gefitinib as a second-line treatment. Conclusions as to the clinical and cost-effectiveness of gefitinib will therefore be limited to the subgroup of patients with EGFR M+ status. Clinical opinion tells us that in the UK most patients who are EGFR M+ receive either erlotinib or gefitinib as a first-line treatment and that a further TKI is unlikely to be administered as a second-line treatment for this group of patients. However, the AG is aware that there is published non-randomised clinical evidence[17,18] which suggests second-line treatment with erlotinib after first-line treatment with gefitinib may yield some

benefits to patients. The AG will fully review this evidence and use it to inform the de novo economic model if appropriate.

Table 1 Decision problem issued by NICE

Interventions	• Erlotinib • Gefitinib
Population	Adults with locally advanced or metastatic NSCLC that has progressed following prior chemotherapy
Comparators	Erlotinib and gefitinib should be compared with each other and with: • Docetaxel • Best supportive care
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisations. If the evidence allows, subgroups such as those defined by histology (squamous/ non-squamous) and EGFR mutation status. The appraisal should consider the implications of mutational testing. The availability of any patient access schemes for the interventions and comparators should be taken into account in the analysis.

5 REPORT METHODS FOR THE SYNTHESIS OF CLINICAL EFFECTIVENESS EVIDENCE

5.1 Search strategy

Trials and systematic reviews will be identified by searching major medical databases such as MEDLINE, EMBASE and the Cochrane Library. In addition, information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including the following: National Research Register and Controlled Clinical Trials.

An example of the search strategy to be used in MEDLINE is presented in Appendix 1.

Attempts to identify further studies will be made by contacting clinical experts and examining the reference lists of all retrieved articles. The submissions provided by manufacturers will be assessed for unpublished data. Citation searches of key articles will be undertaken.

A database of published and unpublished literature will be assembled from systematic searches of electronic sources, contacting manufacturers and consultation with experts in the field. The database will be held in the Endnote X2 software package.

5.1.1 Study selection and inclusion

Two reviewers will independently screen all titles and abstracts of papers identified in the initial search. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained and the relevance of each study assessed according to the inclusion criteria in Table 2. These reflect the criteria described in the final scope issued by NICE.[9] Any discrepancies will be resolved by consensus and if necessary a third reviewer will be consulted. Studies that do not meet all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion. In the event that data from randomised controlled trials (RCTs) are missing or limited, data from non-randomised studies may be used. The identification and use of such data will be described in the final report.

Table 2 Inclusion criteria (clinical effectiveness)

Study design	Randomised controlled trials
Patient population	Adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy
Interventions	Erlotinib Gefitinib
Comparators	Erlotinib Gefitinib Docetaxel Best supportive care
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life
Other considerations	If the evidence allows, subgroups such as those defined by histology (squamous/ non-squamous), performance status and EGFR mutation status

5.1.2 Data extraction strategy

Data relating to both study design and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and if necessary a third reviewer will be consulted. If time allows, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study. An example of a draft extraction form is presented in Appendix 2.

5.1.3 Quality assessment strategy

The quality of the individual clinical-effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted. The quality of the clinical-effectiveness studies will be assessed according to criteria based on CRD's Guidance for undertaking reviews in healthcare.[19] This information will be tabulated and summarised within the text of the report.

5.1.4 Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Where sufficient data are available, treatment effects will be presented as relative risks for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. Relative risks will be presented as forest plots but only pooled when this is statistically and clinically meaningful. Studies will be grouped according to the comparator used. Heterogeneity between the included studies will be assessed by considering differences in (a) the study population, (b) intervention, (c) outcome measures, and (d) study quality. In addition, where

pooling seems appropriate, I^2 tests of heterogeneity will be performed. Where direct comparisons are not possible, if the data allow, indirect comparisons analyses will be conducted.

6 REPORT METHODS FOR THE SYNTHESIS OF COST-EFFECTIVENESS EVIDENCE

6.1 Search strategy

The search strategies detailed in section 5 will be adapted accordingly to identify economic evaluations for inclusion in the cost-effectiveness literature review. At the same time, the search strategy will be used to identify economic evaluations and other information sources which may include data that can be used to populate a de novo economic model where appropriate. Other searching activities, including electronic searching of online health economics journals and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report.

6.1.1 Study selection and inclusion criteria

In addition to the inclusion criteria outlined in Table 2, specific criteria required for the cost-effectiveness review are described in Table 3.

Table 3 Inclusion criteria (cost effectiveness)

Study design	Full economic evaluations that consider both costs and consequences (cost-effectiveness analysis, cost-utility analysis, cost-minimisation analysis and cost benefit analysis)
Outcomes	Incremental cost per life year gained Incremental cost per quality adjusted life year gained

Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of published literature. In addition, any economic models included in the manufacturer submission(s) will be included as appropriate. Studies that do not meet all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion.

6.1.2 Data extraction strategy

Data relating to both study design and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

6.1.3 Quality assessment strategy

The quality of the individual cost-effectiveness studies/models will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the cost-effectiveness studies/models will be assessed according to a checklist updated from that developed by Drummond et al.[20] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[9] The information will be tabulated and summarised within the text of the report.

6.2 Methods for estimating costs, benefits and incremental cost effectiveness ratios

6.2.1 Cost data

The primary perspective for the analysis of cost information will be the NHS and Personal Social Services. Cost data collection will therefore focus on the marginal direct health service costs associated with the interventions. The relevant time horizon of analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. In line with NICE's methods guide,[21] the costs of generic drugs will be taken from sources that reflect nationally available price reductions (for example the British National Formulary and the NHS Electronic Marketing Information Tool [eMIT]). Any patient access schemes in place for erlotinib and gefitinib will be taken into account.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases).

Where appropriate, costs will be discounted at 3.5% per annum, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.[21]

6.2.2 Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. The AG anticipates that the main measure of benefit will be QALYs.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5%, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.[21]

6.3 Modelling

The ability of the AG to construct an economic model will depend on the data available. An analysis of potential patient subgroups and meaningful treatment pathways for each group will be constructed

and discussed with regard to the feasibility of modelling each pathway, and the options for model design to achieve useful cost-effectiveness results. This may be possible within a single decision model, or require multiple models to be developed. Where modelling is appropriate, a summary description of the model(s) and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis will be presented. In addition, the AG will provide an assessment of the model strengths and weaknesses and discuss the implications of using different assumptions in the model(s). Reasons for any major discrepancies between the results obtained from the AG model(s) and the manufacturer model(s) will be explored.

The time horizon will be a patient's lifetime in order to reflect the chronic nature of the disease. Both costs and QALYs will be discounted at 3.5% as recommended by NICE.[21]

A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical-effectiveness review evidence.

If data are available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost effectiveness analysis or cost-minimisation analysis will be undertaken. Any failure to meet the reference case will be clearly specified and justified, and the likely implications will, as far as possible, be quantified.

6.3.1 Sensitivity analysis

If appropriate, sensitivity analysis will be applied to the AG model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision making for specific comparisons (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves).

7 HANDLING THE MANUFACTURER SUBMISSION(S)

All data submitted by the drug manufacturers, received prior to 12th July 2013 (date to be confirmed by NICE), and meeting the set inclusion criteria will be considered for inclusion in the review. Data arriving after this date will only be considered if time constraints allow. Any economic evaluations included in the manufacturer submission(s) will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Following this analysis, if the existing models (manufacturer or published) are not sufficient, de novo or modified versions of any models may be developed. Clarification on specific aspects of the model may be sought from the relevant manufacturer.

Any 'commercial in confidence' data taken from a manufacturer submission will be clearly marked in the NICE report according to established NICE policy and removed from the subsequent submission to the HTA.

8 EXPERTISE IN THIS TAR TEAM AND COMPETING INTERESTS OF AUTHORS

This TAR team will be made up of the following individuals. The panel of clinical experts will be consulted during the review process. The experts will provide insight into a range of issues related to clinical practice, potential patient characteristics that may influence clinical heterogeneity, relevant patient subgroups, model parameter estimates in the absence of economic evidence, as well as additional sources of relevant evidence such as observational studies and patient registries.

Team lead /clinical systematic reviewer	Dr Janette Greenhalgh
Economic modeller	Ms Sophie Beale
Systematic reviewer (economics)	Dr Angela Boland
Medical statistician	Dr Kerry Dwan
Information specialist	Dr Yenal Dundar
Pharmacy advisor	Ms Chris Proudlove
Director	Dr Rumona Dickson
Clinical advisors	Dr Ernie Marshall
	Dr Anna Mullard
	Dr John Green

None of the review team has any competing interests. Any competing interests relating to any external reviewers will be declared in the final report. All correspondence should be sent to the team lead and the director.

Timetable/milestones

Progress report to NETSCC, HTA	26th July 2013
Assessment report	22nd October 2013

9 REFERENCES

1.   National Institute for Health and Clinical Excellence. Erlotinib for the treatment of NSCLC: TA162.   2012 [cited 2013 March]; Available from: http://publications.nice.org.uk/erlotinib-for-the-treatment-of-non-small-cell-lung-cancer-ta162.

2.   National Institute for Health and Clinical Excellence. Gefitinib for the second-line treatment of locally advanced or metastatic non-small cell lung cancer: Terminated Technology Appraisal No. 175. NICE; 2009 [cited 2013 March]; Available from: http://publications.nice.org.uk/gefitinib-for-the-second-line-treatment-of-locally-advanced-or-metastatic-non-small-cell-lung-cancer-ta175.

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11.   National Institute for Health and Clinical Excellence. Pemetrexed for the first-line treatment of non-small cell lung cancer: Technology Assessment TA181.   2009 [cited 2012 December]; Available from: http://guidance.nice.org.uk/TA181/Guidance/pdf/English.

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13.   National Institute for Health and Clinical Excellence. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small cell lung cancer: TA258. NICE; 2012; Available from: http://guidance.nice.org.uk/TA258/Guidance/pdf/English
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15.	National Institute for Health and Clinical Excellence. Erlotinib for the treatment of non-small cell lung cancer: TA162. NICE; 2008 [cited 2013 March]; Available from: http://guidance.nice.org.uk/TA162/Guidance/pdf/English.

16.	National Institute for Health and Clinical Excellence. Pemetrexed for the treatment of non-small cell lung cancer: TA124. NICE; 2007 [cited 2013 March]; Available from: http://guidance.nice.org.uk/TA124/Guidance/pdf/English.

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20.	Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ economic evaluation working party. BMJ. 1996; 313:275-83.

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10 APPENDICES

1 Draft search strategy (Medline)

1   lung.tw.
2   exp Carcinoma, Non-Small-Cell Lung/
3   nsclc.tw
4   (lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.
5   or/1-4
6   gefitinib.tw.
7   iressa.tw.
8   ZD 1839.tw.
9   erlotinib.tw.
10 tarceva.tw.
11 "osi 774".tw.
12 "EGFR TKI".tw.
13 or/6-12
14 5 and 13
15 randomized controlled trial.pt
16 randomized controlled trial/
17 controlled clinical trial.pt.
18   random allocation/
19 Placebos/
20 clinical trial, phase ii/ or clinical trial, phase iii/
21 (randomized or randomly or trial).ti,ab.
22 or/15-21
23 14 and 22
24 animals/ not humans/
25 23 not 24

2 Draft data extraction forms

Clinical effectiveness data will be extracted and entered under the following headings:

Study details

- Author (i.e. Jones et al.)
- Year (i.e. year of publication or date of interim data collection)
- Endnote reference (endnote reference number)
- Study design (summary of study design and details of subgroup analyses [if any])
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration

Intervention details

Data for each intervention will be entered in the following format:

- Intervention (i.e. drug name[s])
- Dose(s) of intervention(s) (dose)

Participant characteristics

Data for each intervention will be entered in the following format:

- Number of participants enrolled (summary or 'not stated')
- Number of participants lost to follow up (summary or 'not stated')
- Average age (mean/median, range, standard deviation) (age)
- Previous treatments
- Disease characteristics (histology, mutation status)

Outcomes: Definitions and measures

- Primary outcome (description of outcome as reported)
- Secondary outcome (description of outcome as reported)
- Adverse effects of treatment (description of outcome as reported)
- Quality of life (description of outcome as reported)

Outcomes: Results

Data for all outcomes specified in the protocol will be entered in the following format:

- Outcome (description of outcome measure)
- Results for intervention (summary or 'not stated')

Economic evaluation data will be extracted as follows:

- Endnote reference (in the form of xyz, no '#')
- Primary source [database, manufacturer submission]
- Author (i.e. Jones et al)
- Date (i.e. year of publication or date of interim data collection)
- Type of economic evaluation [cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis]
- Currency used [$US, $AS, £Sterling …., not stated]
- Year to which costs apply (enter year or not stated)
- Perspective used (e.g. health service, hospital, third party payer, patient, unclear)
- Study population (describe the population characteristics)
- Intervention 1 (description of intervention 1)
- Intervention 2 (description of intervention 2)
- Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of resource use data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of unit cost data [literature, data from actual source, combination of literature and data from actual source, not stated]
- Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected…]
- Clinical outcomes measured and methods of valuation used (summary of outcomes and valuation methods used)
- Cost data handled appropriately (summary of methods used to e.g. discount, inflate)
- Modelling (summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs)
- Outcome measures used in economic evaluations (summary of outcome measures used in economic evaluations e.g. incremental cost effectiveness ratio, net benefit, cost effectiveness acceptability curve)
- Statistical analysis for patient-level stochastic data (summary of analyses used)
- Appropriateness of statistical analysis (comment on appropriateness)
- Uncertainty around cost effectiveness expressed
- Appropriateness of method of dealing with uncertainty around cost effectiveness
- Sensitivity analysis (list summary of analysis)
- Appropriateness of sensitivity analysis (comment on appropriateness)
- Modelling inputs and techniques appropriate
- Author's conclusions (list as in publication)
- Implications for practice (summary of implications)
- Comments (summary of comments)