1. Title of project

Clinical and cost effectiveness of first-line therapy for adult patients with non-small cell lung cancer

2. TAR team

Liverpool Reviews and Implementation Group (LRiG), University of Liverpool

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For details of expertise within the TAR team see section 8.

3. Plain English summary

Non-small cell lung cancer (NSCLC) is a disease that affects almost 40,000 people in the UK each year. The treatment of the disease is hampered by its late diagnosis and very poor response to therapy and subsequently poor patient survival. In 2005 the National Institute for Health and Clinical Excellence (NICE) conducted a technology appraisal that evaluated the effectiveness of a number of drug therapies used to treat the disease. Over the past three to four years NICE has individually appraised a number of new drug treatments and made recommendations for treatment. These treatments have not been examined as a group or compared to each other. This proposal provides a protocol for a systematic review that will bring together the evidence related to the clinical effectiveness of these newer treatments, compared to those recommended in previous reviews as well as providing a re-examination of the cost effectiveness of the newer drug therapies.

4. Background

The most recent comprehensive review of chemotherapy treatment of NSCLC was conducted by Clegg *et al.* in 2002[1] and was integral to the development of the NICE guidelines for the diagnosis and treatment of NSCLC in 2005.[2]

In 2005 the NICE Single Technology Appraisal (STA) process was introduced with the purpose of appraising technologies close to their date of launch to ensure the availability of appropriate technologies within the

NHS as soon as possible. The design of the STA process means that each appraisal examines the use of a single technology for a single clinical indication. As a result, it is possible for several single technologies to be appraised for the same condition over a period of time with no formal link between the appraisals. NSCLC is an example of this and at least four STAs have been proposed or conducted regarding first-line chemotherapy treatments for patients with non-small cell lung cancer (NSCLC) since the inception of the STA process and since the previous comprehensive review of lung cancer treatments conducted by Clegg et al in 2002.[1] In fact the current NICE website lists a total of 13 appraisals that examine the treatment of NSCLC. These are a mix of first- and second- line treatment and comprise appraisals that are complete, have been terminated, delayed or are proposed.[3]

NICE is currently in the process of updating the guidelines related to the diagnosis and treatment of lung cancer.[4] LRiG has been in touch with the former head of the NICE clinical guidelines programme, Dr Fergus MacBeth, who has indicated that a comprehensive review of first-line therapy for NSCLC will not be undertaken as a part of this guideline process but that such a review would complement existing research in this area and that the availability of an up-to-date economic model would add great value. LRiG has contacted Andrew Champion (NCC manager) and Mia Schmidt-Hansen (systematic reviewer working on the update) who confirmed that the update will not include chemotherapy alone because there are so many NICE appraisals being done in the area. The guidelines group are however updating the review on chemoradiation. There are also indications that an updated Cochrane review is due to come out in mid-April 2010 which reviews chemoradiotherapy versus radiotherapy alone and also concurrent versus sequential chemoradiotherapy.

The Liverpool Reviews and Implementation Group (LRiG) has carried out a number of STAs in the area of NSCLC and believes that there is now a need to bring together the disparate clinical and cost effectiveness evidence for first-line treatment of NSCLC in the form of a comprehensive Health Technology Assessment report. We believe that an independent HTA report on chemotherapy and radical chemoradiotherapy for NSCLC will be very useful and will inform both current and future guidelines. This proposed review will assist policy makers in deciding how the newer NSCLC chemotherapy agents (e.g. pemetrexed) fit into the treatment pathway in the NHS in England and Wales.

This document describes the protocol for such a report and is being submitted for consideration as a part of LRiG's current TAR research contract. A decision was taken by LRiG regarding the importance of this project and therefore work on the clinical component of the project has already begun (see timelines below.)

5. Decision problem

Background

Currently, NICE guidelines[2] recommend that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status to improve survival, disease control and quality of life. This should consist of a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin). Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation agent. NICE also recommends that pemetrexed in combination with cisplatin may also be considered as a first-line therapy for patients with locally advanced or metastatic NSCLC who are confirmed as having large cell or adenocarcinoma histology; NICE has three other appraisals in its STA workplan.[5]

The current Scottish Intercollegiate Guidelines Network (SIGN) guideline states that chemotherapy with a platinum-based combination doublet regimen should be considered in all stage IIIB and IV NSCLC patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive chemotherapy. It further states that in these patients, the number of chemotherapy cycles given should not exceed four. No particular chemotherapy doublet or platinum agent is recommended in the guideline.[6]

The European Society for Medical Oncology (ESMO)[7] has published clinical recommendations for the diagnosis, treatment and follow-up of NSCLC. The recommendation for the treatment of stage IV disease states that 'Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms' (p 40).

Epidemiology

Lung cancer is the leading cause of death worldwide, while NSCLC accounts for approximately 80% of all lung cancers diagnosed.[8] The LUCADA database lists the main sub-types of NSCLC as squamous cell carcinoma (33%), adenocarcinoma (25%) and large cell carcinoma (4%), with the remaining 36% being NSCLC 'not-otherwise specified' (NSCLC-NOS).[9]

Over 38,000 people in the England and Wales were diagnosed with lung cancer in 2005 making it the second most commonly diagnosed cancer, after breast cancer, equivalent to more than 100 people per day being diagnosed with lung cancer. The link between smoking and lung cancer is well established: approximately 90% of lung cancer is the result of exposure to tobacco smoke. The link between smoking and poverty has also been proven; making lung cancer a disease that disproportionately affects people in the lowest socio-economic groups.[9,10] Survival from lung cancer is poor. Lung cancer was responsible for approximately 34,000 deaths in 2006 and is the most common cause of cancer death in the UK, accounting for more than one-in-five. Only 7% of lung cancer patients survive over five years after diagnosis.[10]

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages – about two-thirds of patients are not diagnosed until it has reached advanced stages of the disease and is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other developed countries, is low active anticancer treatment rates.[10]

The technology

As outlined above there are several different first-line chemotherapy agents available to patients with NSCLC. In summary, chemotherapy treatments recommended by NICE include platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine; more recently, pemetrexed in combination with cisplatin has also been recommended by NICE for patients with large cell or adenocarcinoma.[2]

In addition, there are a variety of first-line chemotherapy treatments which have been approved by the European Medicines Agency (EMA) for patients with NSCLC that have not yet been appraised by NICE including gefitinib, cetuximab, bevacizumab and erlotinib.[3]

In addition, best supportive care (BSC) and different types of chemo-radiation are also first-line treatments that are available to patients with NSCLC. Current guidelines state that: 'Patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy should be offered sequential chemoradiotherapy' (p. 8).[2]

Objectives of the HTA project

The objectives of the project are to evaluate the clinical and cost effectiveness of first-line therapy for adult patients with locally advanced or metastatic NSCLC.

6. Methods for synthesising clinical effectiveness evidence

Systematic review search strategy – published studies

The following databases will be searched for relevant published literature for the period 1990 to September 2009:

- EMBASE
- MEDLINE
- The Cochrane Library (which includes DARE, HTA and NHS EED).

Searches have been limited to these databases based on the evidence related to searching presented by Royle et al.[11] Details of the search strategies used to explore EMBASE and MEDLINE are available in Appendix A. An update search will be carried out in 2010 to capture trials published during the production of this review.

Where electronic search facilities are available, the conference reports of organisations such as the American Society for Clinical Oncology (ASCO) will be searched for details of conferences and abstracts to identify any relevant studies and if data are available, these will be considered for inclusion in the review.

Bibliographies of previous reviews identified by the search (e.g. Clegg *et al*. 2001[1]) and retrieved articles will be searched for further studies. The NICE website will be searched to identify manufacturers' submissions in this treatment area.

Clinical and statistical reviews of relevant chemotherapy treatments will be sought from the US Food and Drug Administration and the EMEA website will be examined to identify further trial information.

A database of relevant references will be developed using EndNote X3 software package.

Study selection

The citations identified by the search strategy will be assessed for inclusion through two stages. Firstly, two reviewers will independently screen all of relevant titles and abstracts identified via electronic searching to identify potentially relevant studies for inclusion in the review. Secondly, full text copies of these potentially relevant studies will be obtained and assessed independently by two reviewers using the inclusion and exclusion criteria outlined below (Table 1). Any disagreements between reviewers will be resolved by discussion at each stage and, if necessary, a third reviewer will be consulted.

Studies that do not meet all of the inclusion criteria will be excluded and their bibliographic details listed with reasons for exclusion. Ongoing studies that do not report relevant outcomes but meet the inclusion criteria will be listed for future use. 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.

Inclusion criteria

TABLE 1 Inclusion criteria (clinical effectiveness)

Study design	Randomised controlled trials Systematic reviews of randomised controlled trials
Patient population	Chemotherapy naïve adult patients with locally advanced or metastatic non-small cell lung cancer
Interventions	Any first-line chemotherapy treatment currently licensed including: Platinum-based chemotherapy (carboplatin or cisplatin) in combination with docetaxel, gemcitabine, paclitaxel, vinorelbine or bevacizumab Pemetrexed plus cisplatin Single agent therapies including erlotinib, gefitinib and cetuximab Any first-line chemo-radiation therapy
Comparators	It is envisaged that the interventions will be compared with active therapy as described above or best supportive care Comparisons of variation in dosing, timing (including concurrent or sequential) or mode of treatment regimens will also be included even when the intervention and comparator drug are the same
Outcomes	Primary outcomes: Overall survival or Progression free survival Secondary outcomes Response rates Adverse effects Health related quality of life
Other considerations	Only studies published since 1990 in full and with English-language abstract will be included

Data extraction

Data from the included studies will be extracted as detailed below and will include the information listed in Appendix B.

Data relating to population characteristics, study design and outcomes will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on data extraction forms which will be piloted using a sample of included studies. Time permitting, authors and/or sponsors of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed in the report.

Quality assessment

All included studies, will be assessed for methodological quality. The quality of RCTs will be assessed using criteria based on CRD Report No. 4[11] (see Appendix C). Questions 4 and 5 will be adapted to reflect the characteristics of patients with NSCLC.

Data relating to quality assessment will be extracted by one reviewer and independently checked for accuracy by a second reviewer and any disagreements will be discussed; a third reviewer will be consulted, if necessary, to achieve consensus.

Methods of analysis/synthesis

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. The possible effects of study quality on the clinical effectiveness data and review findings will be discussed. Where there are sufficient data, and it is appropriate to do so, meta-analyses will be

performed using the Mantel-Haenszel methodology for a fixed-effect model. The meta-analysis will be carried out using the statistical package Review Manager 4.2. Treatment effects will be presented as weighted mean differences for continuous data.

Heterogeneity between trial results will be tested using a standard chi-squared test, with a threshold value of $p<0.1$, and with the I^2 statistic.[12] Where quantitative heterogeneity is indicated, analysis using a random-effects model will be conducted for comparison with results of fixed-effect analysis to assess the robustness of the model chosen. The DerSimonian and Laird methodology will be used for the random effects model.[13] 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.

For binary outcomes (dichotomous data), where sufficient data are available, relative treatment effects will be presented in the form of odds ratios (OR) and/or relative risks (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used, the standardised mean difference (SMD) will be calculated provided skewness is not too great. For time to event outcomes, log hazard ratios (log HR) will be presented. Data will be pooled only if it is clinically and statistically relevant to do so.

Subgroup analyses will be conducted according to the type of disease (e.g. non-squamous, EGFR+ ect) and age of patients if suitable data are available.

7. Methods for synthesising cost effectiveness evidence

Systematic review of published economic literature – search strategy

The search strategy described in section 6 will be used to identify studies examining the cost effectiveness of first-line chemotherapy for adult patients with NSCLC. The search strategy is designed to meet the primary objective of identifying 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. Searching will be undertaken in MEDLINE and EMBASE as well as in the Cochrane Library, which includes the NHS Economic Evaluation Database (NHS EED). The dates for the searches will be from 1990 September 2009.

Study selection

Titles and abstracts will be examined for inclusion by two reviewers independently. Potentially relevant studies will then be obtained in full text and examined more carefully by two independent reviewers using the economic inclusion criteria outlined in Table 2. Any disagreement will be resolved by consensus, and if necessary a third reviewer will be consulted. Only full economic evaluations (assessing both outcomes and benefits) will be included. However, to supplement findings, additional information on costs and benefits will be collated and discussed in narrative format as appropriate.

Inclusion criteria

TABLE 2 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

Data extraction

Data from the full economic evaluations meeting the inclusion criteria will be extracted into structured tables and will include, but not be limited to, the criteria set out in Appendix D.[4] 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.

Quality assessment

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 included studies will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond and colleagues[4] (see Appendix D). This checklist reflects the criteria used to assess the quality of published economic evaluations as detailed in the methodological guidance developed by the NICE.[12] The information will be tabulated and summarised within the text of the report.

Methods of analysis/synthesis

(i) Cost-effectiveness review of published literature

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

(ii) Development of a de novo economic model

If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of first-line chemotherapy treatments for patients with NSCLC. Where possible, the results will be presented as incremental cost per quality adjusted life year (QALY) ratios.

Methods for estimating costs, benefits and cost effectiveness ratios in the de novo economic model

a. Cost data

The primary perspective for the analysis of cost information will be the NHS and personal social services (PSS). Cost data will therefore focus on the marginal direct health service costs associated with the interventions. If evidence indicates that a societal perspective is required to credibly value all important costs and outcomes, this will be explored and presented in the sensitivity analysis. The relevant time horizon of analysis will be a patient's lifetime in order to reflect the chronic nature of the disease.

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.[12]

b. Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. LRiG anticipates that the main measures of benefit will be increased 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.[12]

c. Modelling

LRiG's ability to construct an economic model will depend on the data available. Where modelling is appropriate, a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis (see Section d below) will be presented. In addition, LRiG will provide an assessment of the model's strengths and weaknesses and discuss the implications of using different assumptions in the model. The time horizon will be a patient's lifetime. Both costs and QALYs will be discounted at 3.5% as recommended by NICE.[12]

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.

d. Sensitivity analysis

If appropriate, sensitivity analysis will be applied to LRiG's 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 etc).

If evidence indicates that a societal perspective is required to value credibly all important costs and outcomes, this will be explored and presented.

8. Expertise in this TAR team

The Liverpool Reviews and Implementation Group (LRiG) was established at the University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance is to conduct Technology Assessment Reviews commissioned by the HTA programme. The team has substantial expertise in systematic reviewing, literature searching, assessing clinical outcomes, economic modelling and health economics, and is well practised in applying this expertise to health technology evaluations. In addition, various members of the team have been involved in recent STA appraisals in the area of NSCLC.

A subset of the LRiG team and local clinicians* have been selected on the basis of the specific expertise they bring to the project to work on this project (Table 3).

TABLE 3 LRiG team and expertise

Team member	Expertise	Contribution
Professor Adrian Bagust	Senior economic modeller	Economic modelling
Angela Boland	Health economics and systematic reviewing	Systematic review of economic evaluation/economic modelling
Tamara Brown	Systematic reviewing	Lead reviewer responsible for project management and systematic review of the clinical effectiveness data including meta-analyses
Ms Rumona Dickson Director of LRiG	Assessing clinical outcomes, systematic reviewing	Input into all aspects of the clinical component of the review
Yenal Dundar	Information specialist, assessing clinical outcomes	Development of the search strategies and input into the clinical components of the review
Emer McKenna*	Clinical/oncology expertise	Data extraction of clinical effectiveness data and input into clinical component of the review
James Oyee	Medical statistician	Assessment of medical statistics
Libby Richards*	Clinical/cancer treatment expertise	Data extraction of clinical effectiveness data and input into clinical component of the review
Carlos Saborido-Martin	Economic modelling	Economic modelling

9. Timetable/milestones

The previous involvement of the LRiG team in the appraisal of a variety of treatments for NSCLC within the STA process brought the LRiG team to the conclusion that there was a need for a full systematic review in this area. LRiG therefore identified local clinicians that were interested in the project and began work on the clinical component of this review during periods when other NICE projects were put on hold or cancelled. Work on this review has therefore begun but has been slow to move forward as other NICE and HTA work took priority. We are now proposing that this work be incorporated into our contracted TAR units for this and the coming year. Timelines for progression of the project are dependent on reviewer feedback and a decision regarding the appropriateness of including the work within our contract. Dates for completion therefore will be negotiated when these other decisions are taken.

Dates (estimated)	Activity
Internally done in January, 2009	Finalisation of protocol
Initial screening began in February, 2009	Screening of titles and abstracts
Completed January 2010	Inclusion/exclusion of full text papers
Commenced July 2009	Data extraction (clinical)
Commenced July 2009	Quality assessment (clinical)
TBC – not yet commenced	Data extraction (cost effectiveness)
TBC - not yet commenced	Quality assessment (cost effectiveness)
TBC - not yet commenced	Data synthesis and economic modelling
TBC	Draft report available for internal peer review
Depending on final HTA approval Provisionally December 2010	Full report submitted

10. Potential peer reviewers

Dr Noelle O'Rourke (Consultant Clinical Oncologist)

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11. References

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12. Appendices

Appendix A: Details of clinical search strategies

Ovid MEDLINE(R) 1990 to March Week 3 2009

		Results
1	randomized controlled trial.pt.	266601
2	controlled clinical trial.pt.	78726
3	randomized.ab.	177144
4	placebo.ab.	110573
5	randomly.ab.	128581
6	trial.ab.	184266
7	or/1-6	579686
8	(animals not (humans and animals)).sh.	3254838
9	7 not 8	525513
10	exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.	18909
11	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18385
12	10 or 11	22812
13	exp Antineoplastic Combined Chemotherapy Protocols/ or *Combined Modality Therapy/ or exp chemotherapy, adjuvant/ or exp Radiotherapy/	182017
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	254221
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20673
16	or/13-15	355832
17	9 and 12 and 16	3045
18	limit 17 to (english language and yr="1990 - 2009")	2594

EMBASE 1990 to 2009 Week 13

		Results
1	Randomized Controlled Trial/	167319
2	randomized.ab.	171365
3	placebo.ab.	106176
4	randomly.ab.	114323
5	trial.ab.	168003
6	controlled clinical trial.pt.	0
7	Controlled Clinical Trial/	58798
8	or/1-7	464615
9	limit 8 to human	396769

		Results
10	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18740
11	exp Lung non Small Cell Cancer/ or nsclc.ti,ab.	22601
12	10 or 11	25216
13	Vindesine/ or Docetaxel/ or Cisplatin/ or Etoposide/ or Paclitaxel/ or Carboplatin/ or Navelbine/	128596
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	220301
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20371
16	exp Cancer Radiotherapy/ or exp Chemotherapy/	225579
17	or/13-16	386860
18	9 and 12 and 17	3521
19	limit 18 to (english language and yr="1990 - 2009")	3034

Appendix B: Details of clinical data extraction

Data extraction will include but may not be limited to:

Study details

- Author/Year/Endnote reference
- Randomisation
- Recruitment
- Funding
- Country
- Power
- Setting
- Population
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Intention to treat analysis done?
- Length of follow-up

Intervention details

- Intervention (i.e. drug name(s) and details)
- Dose of intervention
- Duration of intervention

Participant characteristics

- Number of participants randomised
- Number of participants assessed for primary outcome
- Age
- Sex
- Performance status
- Disease stage
- Were baseline demographics and disease state comparable?

Outcomes

- Overall survival
- Median survival time
- Survival rate

- Progression free survival
- Tumour response rate
- Duration of response
- Quality of life
- Haematological toxicity
- Non-haematological toxicity
- Toxic death

Appendix C: Details of clinical quality assessment

The quality of RCTs will be assessed using criteria based on CRD Report No. 4[13]

1. Was the method used to assign participants to the treatment groups really random?*
2. Was the allocation of treatment concealed?**
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for withdrawals stated?
14. Is there any evidence to suggest that the authors measured more outcomes than they reported?
15. Was an intention to treat analysis included?

*(Computer-generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)

**(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially-numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).

Items will be graded in terms of ✓ yes (item properly addressed), ✗ no (item not properly addressed), ✓/ partially (item partially addressed), **?** unclear or not enough information, or **NA** not applicable

Appendix D: Details of economic data extraction and quality assessment

Cost effectiveness data extraction will include, but not be limited to:

- Type of evaluation and synthesis
- Intervention
- Study population/disease
- Time period of study
- Cost items
- Cost data sources

- Country, currency year
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models
- Cost-effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

Studies of cost effectiveness will be assessed for quality using the following criteria, which is an updated version of the checklist developed by Drummond:[4]

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation and generalisability of results