PROTOCOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182)

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 TITLE OF PROJECT

Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome (review of TA182)

2 TAR TEAM AND LEAD

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

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3 PLAIN ENGLISH SUMMARY

Acute coronary syndromes (ACS) are life-threatening conditions that occur when there is a reduction in the blood supply to the heart. This is usually the result of an artery becoming blocked due to a build-up of fatty deposits. The most common symptoms of ACS are chest pain, nausea, sweating and breathlessness. There are three types of ACS, ST-segment elevated myocardial infarction, non-ST-segment elevated myocardial infarction and unstable angina all of which are diagnosed using electrocardiograms and blood tests. The objective of treatment for a patient with ACS is to restore the blood flow to the heart (revascularisation) and one means of achieving this is with percutaneous coronary intervention (PCI). In PCI, a thin wire with a small balloon is guided through the narrowed part of the affected artery. The balloon is then inflated, compressing the material causing the blockage and widening the artery. A small metal mesh tube (stent) is usually implanted to help keep the artery open. Prior to and following PCI treatment, patients with ACS are prescribed antiplatelet medicines for the purpose of preventing further ACS events. In the UK, three antiplatelet medicines are available for use with PCI: prasugrel, clopidogrel and ticagrelor. This review aims to assess the clinical and cost effectiveness of prasugrel for the treatment of ACS with PCI when compared to clopidogrel or ticagrelor. Evidence for clinical effectiveness will be derived from a systematic review of randomised controlled trials. The key outcomes to be considered are non-fatal and fatal cardiovascular events mortality (from any cause), atherothrombotic events, incidence of repeated procedures, adverse effects of treatment (including bleeding events) and health-related quality of life. The evidence for cost effectiveness will be derived from clinical trials, 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 research question and scope

The remit of this review is to appraise the clinical and cost effectiveness of prasugrel within its licensed indication for the treatment of acute coronary syndromes with percutaneous coronary intervention (review of NICE technology appraisal TA182[1]).

4.2 Background

Acute coronary syndromes (ACS) are life-threatening conditions which comprise a group of clinical symptoms associated with acute myocardial ischaemia with or without infarction.[2,3] These conditions are usually the result of a reduction in blood flow associated with a coronary artery becoming narrow or blocked through atherosclerosis and atherothrombosis. The classic symptom of ACS is chest pain or tightness, other symptoms may include breathlessness, sweating or nausea[4,5] although many people

(particularly women and those with diabetes mellitus) may present with atypical pain or no pain at all.[6-8] In the UK, approximately 18% of people with ACS die before admission to hospital.[3]

There are three main types of ACS diagnosed by electrocardiogram and levels of cardiac enzymes: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). A diagnosis of STEMI indicates that the affected artery is completely occluded resulting in progressive necrosis of the area of heart muscle dependent on the blood supply. [5,9] The diagnosis of NSTEMI indicates partial or temporary blocking of an artery[5,9] with limited tissue damage. In the case of UA, partial or temporary occlusion will be present, but without tissue death. [5,9]

The objective of treatment for STEMI is rapid, complete and sustained revascularisation.[4] The recommended treatment for people with confirmed STEMI is immediate (primary) percutaneous coronary intervention (PCI) to the occluded artery.[5,10] In the PCI procedure, the affected coronary artery is widened using a balloon catheter; a stent is usually implanted to act as a scaffold and hold open the artery wall.[5] The target 'door to balloon time' is 90 minutes.[5] In cases where PCI facilities are not immediately available, treatment with thrombolysis (pharmacological reperfusion) is administered.[11] Where the STEMI persists in spite of thrombolytic treatment, PCI in an appropriately equipped unit would be considered[10,11]

The objective of treatment of NSTEMI and UA is to alleviate pain and anxiety, prevent recurrences of ischaemia and prevent or limit progression to further acute myocardial infarction.[2] People presenting with NSTEMI or UA are assessed for risk of further cardiac events (using risk scores of the Global Registry of Acute Cardiac Events [GRACE[12]]). Those at intermediate to high risk will be recommended for early coronary angiography and revascularisation with PCI if appropriate.[13]

Treatment with antiplatelet therapy is a key element in the management of ACS. Antiplatelet treatment includes aspirin in combination with a thienopyridine (clopidogrel or prasugrel) or a cyclopentyl-triazolo-pyrimidine (ticagrelor). The use of antiplatelet therapy will usually commence with an initial loading dose followed by long-term treatment at a standard daily dose.

4.2.1 Epidemiology

During the period 2011 to 2012, records submitted to the Myocardial Ischaemia National Audit Project database indicate that in England and Wales approximately 79,000 people were diagnosed with a myocardial infarction (MI).[14] The British Cardiovascular Intervention Society audit returns for 2011 record an annual upward trend in the number of PCI procedures performed in England (73,153) and Wales (3293).[15] Of these, 25.1% were for STEMI, 37.2% for NSTEMI/UA and the remainder were for stable angina or other condition.[15] Primary PCI made up more than 95% of revascularisation

treatment for patients with STEMI.[15] The upward trend in PCI procedures is largely due to the increasing number of centres that are able to carry out PCIs and centres extending their services to cover 24 hours.[15]

4.2.2 Current treatment options

The three main antiplatelet treatment options for use with patients with ACS who are to be treated with PCI in England and Wales (prasugrel, clopidogrel and ticagrelor) are described below. A number of NICE guidance documents and guidelines are relevant to these treatments and are described in Table 4-1.

Prasugrel

Prasugrel (Efient, Lilly UK) is a thienopyridine class antiplatelet agent that irreversibly inhibits the $P2Y_{12}$ receptor. It is licensed (co-administered with aspirin) for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI. Prasugrel is available as 5mg and 10mg film coated tablets. Treatment for up to 12 months is recommended. The licensed loading dose is 60mg followed by 10mg as a single daily dose. The use of prasugrel in patients who are over 75 years old is not generally recommended but if treatment is necessary then a reduced daily dose of 5mg should be prescribed. Patients who weigh less than 60kg are recommended to take a reduced daily dose of 5mg.

Clopidogrel

Clopidogrel is a thienopyridine class antiplatelet agent that irreversibly inhibits the $P2Y_{12}$ receptor, an adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes. It is licensed in adults (co-administered with aspirin) for the prevention of atherothrombotic events in patients with ACS and is available as 75mg and 300mg film coated tablets. The licensed loading dose is 300mg followed by 75mg as a single daily dose. A number of generic versions of clopidogrel are available.

Ticagrelor

Ticagrelor (Brilique, Astra Zeneca) is a direct-acting $P2Y_{12}$ receptor antagonist with a different mechanism of action from the thienopyridines. Ticagrelor is a cyclopentyltriazolopyrimidine antiplatelet agent that reversibly binds with the oral ADP receptor. Unlike clopidogrel and prasugrel, ticagrelor does not require metabolic activation. Ticagrelor is licensed (co-administered with aspirin) for the prevention of atherothrombotic events in adult patients with ACS including patients managed medically and those who are managed with PCI or coronary artery bypass grafting. Treatment is recommended for up to 12 months. Ticagrelor is available as 90mg film coated tablets. The licensed loading dose is a single 180mg dose followed by 90mg twice daily..

Table 4-1 Relevant NICE guidance and guidelines

Antiplatelet treatment	NICE guidance/guideline	NICE recommendation
Prasugrel	TA182[1] Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention	Prasugrel (in combination with aspirin) is recommended only when: i) immediate primary PCI for STEMI is necessary; ii) stent thrombosis has occurred during clopidogrel treatment or iii) the patient has diabetes mellitus.
Clopidogrel	CG94[13] The early management of unstable angina and non-ST-segment-elevation myocardial infarction	A 300mg loading dose of clopidogrel should be offered to all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital. Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of NSTEMI. Thereafter, standard care, including treatment with low-dose aspirin alone should be given unless there are other indications to continue dual antiplatelet therapy.
Clopidogrel	CG48[16] Secondary prevention in primary and secondary care for patients following a myocardial infarction	*NSTEMI/UA patients* Treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of NSTEMI. Thereafter, standard care, including treatment with low-dose aspirin alone should be given unless there are other indications to continue dual antiplatelet therapy. *STEMI patients* Patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. Thereafter, standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy.
Clopidogrel	TA152[17] Drug eluting stents for the treatment of coronary heart disease	300mg to 600mg loading dose of clopidogrel Where drug-eluting stents are inserted: clopidogrel plus aspirin for 12 months Where bare metal stents are inserted: clopidogrel plus aspirin for up to 3 months (in clinical practice may be up to 12 months).
Ticagrelor	TA236[18] Ticagrelor for the treatment of acute coronary syndromes (ACS)	Ticagrelor (in combination with low-dose aspirin) for up to 12 months is an option for people with ACS who are to be treated with PCI.

The Assessment Group (AG) is aware that in UK clinical practice, patients undergoing PCI for ACS would routinely receive dual antiplatelet therapy for 12 months.

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 4-2. The intervention to be considered is prasugrel (in combination with aspirin) and the relevant patient population is adults with ACS undergoing primary or delayed PCI. The intervention will be compared with clopidogrel (in combination with aspirin) and ticagrelor (in combination with low-dose aspirin). The outcome measures include non-fatal and fatal

cardiovascular events, mortality (from any cause) atherothrombotic events, incidence of repeated revascularisation procedures, adverse effects of treatment (including bleeding events) and health-related quality of life. Subgroups to be considered (if evidence allows) will be those based on ACS subtype (STEMI, NSTEMI or UA) and the presence of diabetes mellitus. 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.

Table 4-2 Decision problem issued by NICE

Interventions	Prasugrel in combination with aspirin
Population	Patients with ACS undergoing primary or delayed PCI
Comparators	Clopidogrel in combination with low-dose aspirin Ticagrelor in combination with low-dose aspirin
Outcomes	The outcome measures to be considered include: • non-fatal and fatal cardiovascular events • mortality (from any cause • atherothrombotic events • incidence of revascularisation procedures • adverse effects of treatment (including bleeding events) • 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 QALY. 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	If the evidence allows the following subgroups will be considered: people with STEMI, NSTEMI, UA and; people with diabetes mellitus. Guidance will only be issued in accordance with the marketing authorisation. The availability of any patient access schemes for the interventions and comparators should be taken into account in the analysis.

5 REPORT METHODS FOR SYNTHESISING CLINICAL 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 National Research Register and Controlled Clinical Trials.

An example of the draft 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 X5 software package.

5.1.1 Study selection and inclusion

Two reviewers will independently screen all titles and abstracts of papers identified in the search. Full text manuscripts of any titles/abstracts that may be eligible for inclusion will be and the relevance of each study assessed according to the inclusion criteria in

Table 5-1. 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 key criteria described in

Table 5-1 (design, patient population, interventions and comparators) 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 5-1 Inclusion criteria (clinical effectiveness)

Study design	Randomised controlled trials
Patient population	Adults with ACS undergoing primary or delayed PCI
Interventions	Prasugrel in combination with aspirin
Comparators	Ticagrelor in combination with aspirin Clopidogrel in combination with aspirin
Outcomes	At least one of the following: Non-fatal and fatal cardiovascular events Mortality from any cause Atherthrombotic events Incidence of revascularisation procedures Adverse effects of treatment (including bleeding events Health-related quality of life
Other considerations	If the evidence allows, the following subgroups will be considered: people with STEMI, people with NSTEMI, people with diabetes mellitus

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 Centre for Review and Dissemination's Guidance[19] for undertaking reviews in healthcare.

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, mean differences for continuous data or as hazard ratios where appropriate along with 95% confidence intervals. Data 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, forest plots will be visually assessed for the presence of heterogeneity, the Chi-squared test will be performed ($p<0.1$) and the I^2 statistic will be calculated to

quantify inconsistency. Where direct comparisons are not possible, if the data allow, indirect comparisons analyses will be conducted.

6 METHODS FOR SYNTHESISING COST EFFECTIVENESS EVIDENCE

6.1 Search strategy

The search strategies detailed in Section 5 will 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 5-1, specific criteria required for the cost-effectiveness review are described in Table 6-1.

Table 6-1 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 and/or 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.[21] The information will be tabulated and summarised within the text of the report.

6.1.4 Methods of analysis

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.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the manufacturer submission(s) to NICE, will be collated and presented as appropriate.

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 (e.g. the British National Formulary and the NHS Electronic Marketing Information Tool [eMIT]). Any patient access schemes in place 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, with the type of economic evaluation 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 option 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 SUBMISSIONS

All data submitted by the drug manufacturers, received prior to 18th September 2013, 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 report prepared for NICE according to established NICE policy and removed from the subsequent submission to the HTA.

8 EXPERTISE IN THIS TAR TEAM AND COMPETING INTERESTS

This TAR team will be made up of the following individuals. A 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	Professor Adrian Bagust
Systematic reviewer (economics)	Dr Angela Boland
Medical statistician	Dr Kerry Dwan
Information specialist	Dr Yenal Dundar
Director	Dr Rumona Dickson
Pharmacy Advisor	Ms Christine Proudlove
Clinical Advisor	Dr Michael Fisher

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.

9 PROJECT TIMELINES

Table 9-1 Timetable/milestones

Progress report to NETSCC, HTA	25th September 2013
Assessment report	18th December 2013

10 REFERENCES

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11 APPENDICES

1 Draft search strategy (MEDLINE)

1	exp Acute Coronary Syndrome/
2	exp Angina, Unstable/
3	(unstable adj2 angina).ti,ab.
4	exp Myocardial Infarction/
5	(myocardial adj infarction).ti,ab.
6	heart infarct$.ti,ab.
7	exp Myocardial Ischemia/
8	myocardial isch?em.ti,ab.
9	(isch?emic adj3 heart).ti,ab.
10	(coronary adj2 syndrome$).ti,ab.
11	exp Coronary Artery Disease/
12	((coronary or isch?em$) adj2 (heart or artery)).ti,ab.
13	or/1-12
14	(Prasugrel or Effient or Efient).af.
15	(Ticagrelor or Brilinta or Brilique or Clopidogrel or Plavix).af.
16	14 and 15
17	13 and 16
18	limit 17 to (english language and humans)

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)