Date: 11 August 2009

1. Title of the project:

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90)

2. TAR team and 'lead'

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3. Plain English Summary

Occlusive vascular events (OVEs) are the result of a reduction in blood flow related to the narrowing or blocking of an artery which is usually caused by atherosclerosis and atherothrombosis. Occlusive vascular events include transient ischaemic attack (TIA), ischaemic stroke and myocardial infarction (MI). Peripheral arterial disease (PAD) is also caused by narrowing of arteries. Peripheral artery disease may be asymptomatic but commonly presents with leg pain on walking (intermittent claudication). People with PAD are at high risk of OVEs including MI, stroke or TIA.

The remit of this appraisal is to review and update (if necessary) the evidence base of technology assessment report TA90: the clinical and cost-effectiveness of clopidogrel and modified-release dipyridamole (MRD) (alone or in combination with aspirin), within their licensed indications, for the prevention of OVEs in patients with established PAD, or with a history of MI, ischaemic stroke, or TIA.

A systematic review of evidence from randomized controlled trials (RCTs) and manufacturer submissions will consider the key clinical outcomes of: MI, unstable angina, stroke, death, vascular death, adverse effects of treatment (including bleeding complications); health-related quality of life (QoL). The evidence for cost effectiveness of treatments will be derived from clinical trial evidence as well as modelling studies and other data sources. Cost effectiveness will be expressed in terms of incremental cost per quality adjusted life years (QALYs). Costs will be considered from an NHS and Personal Social Services perspective.

4. Decision problem

Occlusive vascular events are the result of a reduction in blood flow related to the narrowing or blocking of an artery which is usually caused by atherosclerosis and atherothrombosis. These OVEs include transient ischaemic attack (TIA), ischaemic stroke and myocardial infarction (MI). Peripheral arterial disease (PAD) is also caused by narrowing of arteries. Peripheral artery disease may be asymptomatic but commonly presents with leg pain on walking (intermittent claudication). People with PAD are at high risk of OVEs, including MI, stroke or TIA.[1]

Annually, between 94,000 and 117,000 people experience a stroke episode in England and Wales and a further 20,000 people have a TIA. Stroke accounts for 11% of deaths in England. Stroke is also the leading cause of disability in adults. In the UK, annually, around 259,500 people experience an acute MI, an event that is associated with high morbidity and mortality; around 30% of people die from their first MI. Approximately 20% of people aged 55 to 75 years have evidence of lower extremity

PAD. Five percent of this population appears to have symptoms with the most common being intermittent claudication. Since the UK population aged 55 years or older is approximately 17 million, this equates to a prevalence of around 850,000 with intermittent claudication.[1] NICE guidance (TA90)[2] on clopidogrel and MRD in the prevention of OVEs makes the following recommendations: for people who have had an ischaemic stroke or a TIA: the use of MRD in combination with aspirin is recommended for a period of two years from the most recent event. Thereafter, or if MRD is not tolerated, patients should revert to standard care which includes the use of long-term, low-dose aspirin. People with OVEs or PAD and who are intolerant to low-dose aspirin are advised to use clopidogrel alone (within its licensed indications).

The remit of this appraisal is to review and update (if necessary) the clinical and cost-effectiveness evidence base described in TA90[2] which focused on clopidogrel and MRD (alone or in combination with aspirin), within their licensed indications, for the prevention of OVEs in patients with established PAD, or with a history of MI, ischaemic stroke or TIA.

Clopidogrel is licensed in adults for the prevention of atherothrombotic events in patients suffering from MI (from a few days up until 35 days), ischaemic stroke (from 7 days up until 6 months) or established PAD. [3] (Clopidogrel use in acute coronary syndromes is not within the remit of this review). [1]

Modified-release dipyridamole is licensed, alone or in combination with aspirin, for secondary prevention of ischaemic stroke and TIAs. [4] A combination product containing MRD and standard-release aspirin is also available for the same indication.[2]

[1] License does not include use in patients with TIA

[2] Among other properties, dipyridamole acts as a potent vasodilator. It should therefore be used with caution in patients with severe coronary artery disease including unstable angina and/or recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).

Table 1 Decision problem issued by NICE 2009[1]

Patient population	Patients with established peripheral arterial disease or those with a history of myocardial infarction, ischaemic stroke or transient ischaemic attacks.
Interventions	Clopidogrel
	Modified-release dipyridamole used alone or in combination with aspirin
Comparators	The interventions will be compared with aspirin and, where appropriate, with each other
Outcomes	• Myocardial infarction (STEMI and NSTEMI) • Unstable angina • Stroke • Vascular death • Death • Adverse effects of treatment including bleeding complications • 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.

The patient population, interventions, comparators and outcomes as set out in the decision problem in the scope issued by NICE[1] are described in Table 1. The population of interest is patients with established PAD, or those with history of MI, ischaemic stroke or TIA. (In addition, if the evidence allows, the clinical effectiveness of clopidogrel in people with multi-vascular disease (patients with atherosclerotic disease in more than one vascular location) who are considered to be at high risk of recurrent OVEs will be assessed, as will the duration of treatment with the interventions.) The cost effectiveness of treatments will be expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost effectiveness will 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.

5. Report methods for the synthesis of clinical effectiveness

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. The search strategy will be adapted from that used in the existing TA90[2] review, a sample of which is presented in Appendix 1. In order to update the review, dates of new searches will be from April 2003 up to and including August 2009. New data will be incorporated with data from the previous appraisal.

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, hand searching, contacting manufacturers and consultation with experts in the field. The database will be held in the Endnote X2 software package.

Inclusion criteria

Table 2 Inclusion criteria (clinical effectiveness)

Study design	Randomised controlled trials Systematic reviews
Patient population	For clopidogrel, adults with established peripheral arterial disease or those with a history of myocardial infarction or ischaemic stroke.
	For MRD, adults with a history of ischaemic stroke or transient ischaemic attacks will be included.
Interventions	Clopidogrel
	Modified-release dipyridamole used alone or in combination with aspirin
Comparators	The interventions will be compared with aspirin and, where appropriate, with each other
Outcomes	Any of the following: • Myocardial infarction (STEMI and NSTEMI) • Unstable angina • Stroke • Vascular death • Death • Adverse effects of treatment including bleeding complications • Health related quality of life
Other considerations	If the evidence allows, the effectiveness of clopidogrel in people with multi-vascular disease (patients with atherosclerotic disease in more than one vascular location) who are considered to be at high risk of recurrent occlusive vascular events, will be considered If the evidence allows, the duration of treatment with the specified interventions will be considered.

The inclusion criteria were selected to reflect the criteria described in the final scope issued by NICE.[1]for the review and are described in Table 2. 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 above. 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 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.

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.

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 Report No. 4[5] (see Appendix 3). This information will be tabulated and summarised within the text of the report.

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.

6. Report methods for synthesising evidence of cost effectiveness

The inclusion criteria for the cost-effectiveness review are shown in Table 3. The literature review of economic evidence will include the quality assessment of published cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses. Economic model(s) included in the manufacturer submission(s) will be critiqued as appropriate.

If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of clopidogrel and MRD for the prevention of OVEs.

The likely budget impact that would arise for the NHS in England and Wales will also be estimated. This budget impact will take account of available information on current and anticipated patient numbers and service configuration for the treatment of this condition

Search strategy

The search strategy will be 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 April 2003 up to and including August 2009.

Inclusion and exclusion

Table 3 Additional 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

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

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.

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[6] (see Appendix 3). This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[7]The information will be tabulated and summarised within the text of the report.

Methods of analysis/synthesis

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.

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.

Methods for estimating costs, benefits and cost effectiveness ratios

a. Cost data

The primary perspective for the analysis of cost information will be the NHS and personal social services. 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.

It should be noted that in May, 2009 the Committee for Medicinal Products for Human Use (CHMP) provided positive opinions for six generic versions of clopidogrel.[8] The implications of change in costs of these new generic products will be included in the assessment report.

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.[7]

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.[7]

c. Modelling

The ability of LRiG 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) 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. Reasons for any major discrepancies between the results obtained from assessment group model 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.[7]

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.

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.

7. Handling the manufacturer submission(s)

All data submitted by the drug manufacturers received prior to 23rd October 2009 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. Competing interests of authors

Review team members

Team lead /clinical systematic reviewer	Dr Janette Greenhalgh
Senior economic modeller	Professor Adrian Bagust
Systematic reviewer (economics)	Dr Angela Boland
Economic modeller	Dr Carlos Martin Saborido
Information specialist	Dr Yenal Dundar
Director	Ms Rumona Dickson
Clinical advisor	Dr Michael Fisher

Dr Michael Fisher (Royal Liverpool Hospital) has received remuneration from Bristol Myers Squibb/Sanofi for consultancy, symposium attendance, organising education, speaking and staffing. No other member of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

References

1. National Institute for Health and Clinical Excellence. Final scope for the appraisal of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of TA 90). 2009.
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8. European Medicines Agency. Committee for Medicinal Products for Human Use - May 2009 Plenary Meeting Monthly Report. London2009 [cited 2009 August]; Available from: http://www.emea.europa.eu/pdfs/human/comp/pr/28196709en.pdf.

9. Appendices

Appendix 1: draft search strategy

MEDLINE (Ovid)

1 randomized controlled trial.pt.

2 randomized controlled trials/

3 randomi?ed controlled trial$.ti,ab.

4 random allocation/

5 double-blind method/

6 single-blind method/

7 (clin$ adj2 trial$).ti,ab.

8 ((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab.

9 placebos/

10 placebo$.ti,ab.

11 random.ti,ab.

12 exp RESEARCH DESIGN/

13 comparative study/

14 exp evaluation studies/

15 follow-up studies/

16 prospective studies/

17 (control or controls or controlled).ti,ab.

18 clinical trials, phase iv/

19 phase iv.ti,ab.

20 phase four.ti,ab.

21 phase 4.ti,ab.

22 post market$ surveillance.ti,ab.

23 or/1-22

24 Ticlopidine/

25 clopidogrel.ti,ab.

26 plavix.ti,ab.

27 90055-48-4.rn.

28 asasantin retard.ti,ab.

29 persantin retard.ti,ab.

30 dipyridamole.ti,ab.

31 dipyridamole/

32 58-32-2.rn.

33 or/24-32

34 exp MYOCARDIAL INFARCTION/

35 (myocard$ infarc$ or MI).ti.

36 NSTEMI.ti,ab.

37 non ST segment elevation myocardial infarction.ti,ab.

38 stroke.ti.

39 CEREBROVASCULAR ACCIDENT/

40 (cerebrovascular accident$ or CVA).ti.

41 ISCHEMIC ATTACK, TRANSIENT/

42 (isch?emic stroke or transient isch?emic attack$).ti,ab.

43 ANGINA, UNSTABLE/

44 unstable angina.ti,ab.

45 peripheral arterial disease.ti,ab.

46 (TIA or TIAS).ti.

47 or/34-46

48 23 and 33

49 47 and 48

Appendix 2: 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)
- Definition of high risk group (if any?) (summary or 'not stated')
- 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 of intervention (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')
- Mean age (range, standard deviation) (age(s))
- Qualifying event (summary of participants presenting with e.g. MI, ischaemic stroke, TIA, PVD or 'not stated')

Data on prognostic indicators will be entered under the following headings:

- Myocardial infarction (summary or 'not stated')
- Stroke (summary or 'not stated')
- Heart failure (summary or 'not stated')
- Hypertension (summary or 'not stated')
- Current or former smoker (summary or 'not stated')
- Diabetes (summary or 'not stated')
- Other (summary of other reported prognostic indicators or 'not stated')

Concomitant medication

- Medication before randomisation (summary or 'not stated')
- Medication after randomisation (summary or 'not stated')

Outcomes: Definitions and measures

- Primary outcome (description of outcome as reported)
- Secondary outcome (description of outcome as reported)
- Bleeding complications (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')

Adverse events

- Bleeding complications (summary or 'not stated')
- Other adverse events (summary or 'not stated')

Economic evaluation data will be extracted as follows:

- Endnote reference (in the form of xyz, no '#')
- Primary source [database, handsearching, 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, societal, 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)

Appendix 3: Quality Assessment Scales

Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4[5]:

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 prognostic factors?
5. Was baseline comparability achieved in terms of prognostic factors?
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

Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond[6]**:**

Study question

1. Costs and effects examined
2. Alternatives compared
3. The viewpoint(s)/perspective of the analysis is clearly stated *(e.g. NHS, society)*

Selection of alternatives

4. All relevant alternatives are compared *(including do-nothing if applicable)*
5. The alternatives being compared are clearly described *(who did what, to whom, where and how often)*
6. The rationale for choosing the alternative programmes or interventions compared is stated

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated
(*e.g. single study, selection of studies, systematic review, expert opinion*)
10. Effectiveness data from RCT or review of RCTs
11. Potential biases identified (especially if data not from RCTs)
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)

Costs

13. All the important and relevant resource use included
14. All the important and relevant resource use measured accurately (with methodology)
15. Appropriate unit costs estimated (with methodology)
16. Unit costs reported separately from resource use data
17. Productivity costs treated separately from other costs
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated
(*cases detected, life years, QALYs, etc.*)
20. Methods to value health states and other benefits are stated (e.g. *time trade off*)
21. Details of the individuals from whom valuations were obtained are given
(*patients, members of the public, health care professionals etc.*)

Decision modelling

22. Details of any decision model used are given (e.g. *decision tree, Markov model*)
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified
24. All model outputs described adequately.

Discounting

25. Discount rate used for both costs and benefits
26. Do discount rates accord with NHS guidance (1.5%-2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and confidence intervals are given for stochastic data
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis etc*)
35. The choice of variables for sensitivity analysis is justified
36. The ranges over which the variables are varied are stated

Presentation of results

37. Incremental analysis is reported using appropriate decision rules
38. Major outcomes are presented in a disaggregated as well as aggregated form
39. Applicable to the NHS setting

All items will be graded as either ✓ yes (item adequately addressed), ✕ no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.