Protocol for rapid review of the clinical effectiveness and cost-effectiveness of single photon computed emission tomography (SPECT) myocardial perfusion scintigraphy (MPS) for the diagnosis and management of coronary heart disease

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B. Details of review team

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Steering Committee: Professor John Cairns, Professor Peter Fayers, Professor Adrian Grant, Professor Phil Hannaford, Professor W. Cairns Smith, Professor Norman Waugh.

C. Full title of research question

Systematic review of the clinical effectiveness and cost-effectiveness of single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy (MPS) for the diagnosis and management of coronary heart disease.

D. Clarification of research question and scope

This review will assess the clinical effectiveness and cost-effectiveness of SPECT MPS for the diagnosis of patients with suspected coronary heart disease and the prognosis and management of patients with diagnosed coronary heart disease.

The analysis will focus on the value of SPECT MPS in clinical care. Costs and cost-effectiveness will be assessed from the perspective of the NHS and Personal Social Services.

If the evidence allows, the review will attempt to:

- estimate the diagnostic accuracy of SPECT MPS compared with stress ECG and coronary angiography (CA);
- determine the role of SPECT MPS in the risk assessment (prognosis) of patients with coronary artery disease and in particular of patients with myocardial infarction;
- evaluate the role of SPECT MPS in pre-operative risk assessment of patients undergoing major surgery who are potentially at risk of coronary events;
- evaluate the role of SPECT MPS in monitoring the effects of revascularisation;
- evaluate the use of SPECT MPS in the context of rapid access chest pain clinics, and consider the implications for referral routes within the health services;
- evaluate the role of electrocardiography (ECG)-gated SPECT;
- identify the criteria for selecting patients for whom SPECT MPS would be particularly appropriate.

The implications to the NHS in terms of service provision, waiting times and training will be highlighted.

The use of MPS for assessing myocardial viability will not be examined. No comparisons, in terms of their effectiveness and cost-effectiveness, will be made between different radionuclides, or between different pharmacological agents for inducing stress, or between exercise and pharmacological stress, or between early and delayed imaging.

Magnetic resonance techniques, positron emission tomography or stress echocardiography will not be examined.

E. Report methods

E.1 Search strategy

Extensive electronic searches of the databases listed in Table 1 will be conducted to identify both published and unpublished studies. These searches will aim to identify primary studies evaluating the effectiveness and cost-effectiveness of SPECT MPS as part of the stress ECG/SPECT/coronary angiography clinical pathway. The searches will cover the period from 1980 to October/November 2002.

Table 1. Databases to be searched

Database	Years to be searched
Medline	1980 – October 2002
Embase	1980 – October 2002
Biosis	1985 – October 2002
Science Citation Index	1981 – October 2002
PreMedline	October 2002
Cochrane Controlled Trials Register	Cochrane Library 2002 Issue 4
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library 2002 Issue 4
Database of Abstracts of Reviews of Effectiveness (DARE)	November 2002
CRD NHS EED	November 2002
Health Management Information Consortium	1979-2002
National Research Register	Issue 4 2002
ReFeR	November 2002

In addition, current research registers will be searched and the reference lists of all included studies will be scanned.

Potentially relevant non-English language studies will be noted but excluded from the review, unless relevant data are reported in an English language abstract.

E.2 Inclusion criteria

E.2.1 Types of studies

Primary prospective studies (i.e. randomised controlled trials, controlled clinical trials, comparative observational studies) and primary retrospective studies (i.e. comparative observational studies) of SPECT MPS compared with any of the interventions noted in E.2.3 below for the diagnosis, prognosis, risk assessment, stratification and management of patients with suspected or confirmed coronary heart disease, will be included.

The following kinds of reports will not be considered: case reports; pictorial essays; pilot, volunteer, phantom, animal or safety studies; studies investigating technical aspects of SPECT MPS or the development of imaging acquisition and processing.

E.2.2 Population

Adults with suspected or diagnosed coronary heart disease will be included, with the exception of pregnant women. If the evidence allows, subgroup analysis will be undertaken on:
(a) patients who have experienced previous myocardial infarction; and,
(b) women.

We will exclude studies evaluating patients who have received heart transplants, studies evaluating patients with hypertrophic cardiomyopathy, mitral valve prolapse, primary aldosteronism, lupus, acromegaly, cystic fibrosis, severe obstructive sleep apnoea, sickle-beta-thalassemia, and studies evaluating patients following aortic reconstruction.

E.2.3 Types of interventions

The interventions included will be:

- SPECT (including ECG-gated SPECT and attenuation-corrected SPECT) as part of the clinical care pathways. Planar imaging will be excluded. The types of radionuclide tracers to be considered will be limited to thallium-201, technetium-99m sestamibi or technetium-99m tetrofosmin. Stress may be induced by exercise (treadmill/bicycle) or pharmacologically (adenosine/dipyridamole/dobutamine) or by a combination of exercise and pharmacological means.
- Stress ECG.
- Coronary angiography.

For studies of diagnostic accuracy the interventions will be:

- Stress ECG and SPECT, with coronary angiography as the reference standard. In situations where coronary angiography would be an inappropriate reference standard (for example patients with mild clinical symptoms), clinical follow-up will be accepted as the reference standard.

In the event that insufficient data on diagnostic accuracy are identified by the above strategy, studies of diagnostic accuracy of SPECT alone with coronary angiography as the reference standard, or of stress ECG alone with coronary angiography as the reference standard, will be considered.

For prognostic studies, the interventions will be:

- The stress ECG/SPECT/CA clinical pathway with and without SPECT, for example:
    - Stress ECG and SPECT and CA compared with stress ECG and CA; or,
    - Stress ECG and SPECT compared with stress ECG alone; or,
    - SPECT and CA compared with CA alone; or,
- Stress ECG and SPECT and coronary angiography; or,
- SPECT and coronary angiography; or,
- Stress ECG and SPECT.

In the event that insufficient data are identified by the above strategy, studies of SPECT with clinical follow-up, but without stress ECG or coronary angiography as a comparator, will be considered.

Studies of SPECT compared with ECG-gated SPECT or attenuation-corrected SPECT (in any combination) will be included.

E.2.4 Types of outcome measures

1. For studies of diagnostic accuracy, either the absolute numbers of true positives, false positives, false negatives, true negatives, or the sensitivity and specificity values.

2. For studies of prognosis, risk assessment, stratification and patient management:

- mortality;
- cardiac mortality;
- nonfatal myocardial infarction (MI);
- revascularisation;
- occurrence of unstable angina;
- other major cardiac events;
- survival free of cardiac death;
- preservation of left ventricular function (after surgery);
- post-operative complications;
- number of coronary angiographies performed;
- hospital admissions;
- quality of life measures.

E.3 Data extraction strategy

The titles and abstracts (if available) of all papers identified by the search strategy will be screened. We will obtain full text copies of all studies deemed to be potentially relevant and two reviewers will independently assess them for inclusion. Reviewers will not be blinded to the names of studies' authors, institutions or publications. Any disagreements will be resolved by consensus or arbitration.

We will develop and pilot a data extraction form. Two reviewers will independently extract details of study design, methods, participants, interventions, testing procedures, outcomes and follow-up. In addition, we will record the type of stress test performed, the type of radionuclide used, the authors' definitions of coronary artery disease (for example ≥ 50% stenosis or ≥ 70% stenosis), the authors' definition of a positive stress ECG test (for example at least 0.1 mV horizontal or downsloping ST-segment depression measured 80 ms after J point), the percentage of men/women included in the study, the percentage of patients in the study with previous myocardial infarction and/or who have undergone cardiac surgery. Any disagreements will be resolved by consensus or arbitration.

E.4 Quality assessment strategy

Two reviewers will independently assess the quality of all included studies, using an assessment form developed for this purpose. The following criteria, assessing the internal and external validity of diagnostic studies, will be applied: valid reference standard, verification bias, blind assessment of index and reference standard, index test interpreted independently from other clinical information, spectrum of disease, characteristics of patients, performance of index test and reference standard. The quality of prognostic studies will be assessed in terms of the definition and selection of patient sample, length of follow-up, outcome criteria, and adjustment for significant prognostic factors. Any disagreements will be resolved by consensus or arbitration.

E.5 Methods of analysis/synthesis

For studies of diagnostic accuracy, we will tabulate the results of each individual study in a 2 x 2 table, an example of which is shown in Table 2. For each study we will calculate sensitivity, specificity, likelihood ratios for a positive and negative test result, and diagnostic odds ratios. The sensitivities and specificities will be plotted on summary receiver operating characteristic (ROC) curves. Summary ROC curves will be generated, where possible, for each testing procedure.

Table 2. Example of 2 x 2 table

	Target Disease	
	Present +	**Absent -**
Test Positive +	a	b
Test Negative -	c	d

If included studies use different thresholds to define positive and negative test results, the likelihood of a possible threshold effect will be investigated either graphically by means of a summary ROC curve or statistically by assessing the heterogeneity of sensitivities and specificities and examining a possible relationship between them. To ascertain whether certain factors might affect the accuracy of SPECT MPS we will calculate the summary ROC curve taking account of the following variables: the methodological quality of included studies (for example good quality/poor quality studies), the clinical definition used of coronary artery disease, whether the study participants consisted solely of women, and whether participants with previous myocardial infarction were excluded. If results from the primary studies prove to be homogeneous and display no threshold effect, the pooled weighted means of sensitivities, specificities or likelihood ratios and their 95% confidence intervals will be calculated using a fixed effects model. Pooled weighted results will also be generated separately for important patient subgroups (for example patients with previous myocardial infarction). If heterogeneity is present amongst the primary studies, we will consider whether to limit the analysis to homogeneous subgroups of patients and to employ a random effects model. However, if pooling of data proves to be not feasible or appropriate, we will present a qualitative synthesis of the results of the included primary studies.

For studies of prognosis, risk assessment, stratification and patient management, outcomes of individual primary studies will be tabulated and confidence intervals calculated around the measure of prognosis. If appropriate, a quantitative synthesis will be attempted using standard meta-analytic techniques.

E.6 Methods for estimating quality of life, costs and cost-effectiveness and/or cost per QALY

A two-stage process will be used to assess the relative efficiency of SPECT. The first stage will consist of a systematic review of available economic evaluations, including those submitted by Industry. The economic evaluations will be identified using the search strategy outlined in section E.1 above and their quality assessed using a 10-point checklist.[1] Strengths and weaknesses in terms of methodology adopted, reporting of results and conclusions will be described. A narrative summary of results will be provided. Where results differ between the identified economic evaluations, potential causes will be identified and discussed.

In the second stage a model will be developed to estimate the relative cost-effectiveness of SPECT. This model will combine data on clinical effectiveness with cost data relevant to the UK NHS and Personal Social Services. The model will be constructed by following the stages outlined below:

1. Identification of all main event pathways that have distinct resource implications or outcome values associated with them;
2. Estimation of the probabilities associated with the main event pathways, both for resource use and outcomes;
3. Descriptive data to enable the resource consequences associated with each pathway to be measured; and,
4. Descriptive data (unit costs and utilities) to enable the outcomes associated with following each pathway to be valued.

The model will be used to estimate costs and effectiveness for a cohort of patients with suspected or diagnosed coronary heart disease for the different diagnostic/prognostic strategies adopted. The precise nature of the model will be constrained by the data available. The type of economic evaluation will depend upon the findings. Where one strategy is found to be both more beneficial and more costly then the results will ideally be presented in terms of incremental cost per quality adjusted life year (QALY). If insufficient data are available to construct QALYs then the results will be presented in terms of cost per unit of natural or clinical measure of outcome, such incremental cost per life year gained or other relevant outcome as determined by the results of the review of the effectiveness data, and as a balance sheet.

Possible diagnostic/prognostic strategies include:

- stress ECG followed by SPECT then coronary angiography. Use of SPECT and coronary angiography would be determined by the results of the preceding test;
- stress ECG and SPECT followed by coronary angiography where indicated by the results of the preceding tests;
- stress ECG followed by coronary angiography where indicated by the results of the preceding test.

The possible diagnostic/prognostic strategies and their associated event pathways will be based on clinical advice and data from the literature. The data on probabilities, resource use, cost and utilities (stages 2 to 4 in E.6) will be obtained using the methods outlined below.

E.6.1 Probabilities that the events described in the event pathways will occur

The principal sources of data will be the outcomes of the systematic review of effectiveness data described in E.2.4.

E.6.2 Cost data

The primary perspective for the costing will be the NHS and Personal Social Services. Cost data will therefore include the direct health service costs associated with the alternative diagnostic/prognostic strategies.

Quantities of resources used will be identified from consultation with experts, the reviewed literature and primary data collection. We anticipate that unit cost data will be extracted from the literature or obtained from other relevant sources (for example manufacturer price lists, NHS reference costs). All cost data will be converted to a single year (2002) in pounds sterling.

The following data will be needed to estimate costs incurred by the NHS for a particular procedure:

- Set-up costs of establishing appropriate facilities;
- Staff time costs, consumables, overheads and capital charges associated with the procedures used;
- Management of any complications that may occur;
- Cost consequences of the management strategy adopted.

Where appropriate costs will be discounted at 6%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

E.6.3 Assessment of benefits

Using data from the review of effectiveness, estimates will be made of survival, the overall frequency of cardiac events and procedures.

If at all possible, QALYs will be estimated for the different diagnostic strategies. The strengths and weaknesses of the sources used to compute these QALY values will be highlighted. The utility weights underlying the estimates of QALYs will be obtained from quality of life estimates obtained from the literature (see E.2.4 above) and other sources, for example the Harvard cost-effectiveness registry (http://www.hsph.harvard.edu/cearegistry/).

Where appropriate, effectiveness and other measures of benefit will be discounted at 1.5%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

E.6.4 Sensitivity analysis

Sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. Where the overall results are sensitive to a particular variable, the sensitivity analysis will be reported.

Finally, the results of the evaluation will be used to estimate the total NHS cost implications under different scenarios of adoption of SPECT, such as the different subgroups outlined in E.2.2 above.

F. Handling the company submission(s)

We will develop the economic model to assess cost-utility and cost-effectiveness, using if necessary data contained in the company submission(s) to inform the estimates of effectiveness, cost-effectiveness and cost-utility. As stated in E.6 above, any economic models contained within the company submission(s) will be assessed using the Drummond 10-point checklist.[1] Strengths and weaknesses in terms of methodology adopted, reporting of results and conclusions will be described. It will then be compared with the results provided by the model we develop so that differences in results can be highlighted. If the model we develop differs substantively from that put forward by any company, we will justify any assumptions made. Any 'commercial in confidence' data taken from the company submission(s) will be <u>underlined</u> in the HTA report (followed by an indication of the relevant company name in brackets) so that the NICE secretariat can negotiate (before and during the Institute's consultation process) with industry the subsequent inclusion of such data in the HTA monograph publication or subsequent peer-review publications.

G. Project management

G.1 Timetable/milestones

Draft protocol: 1 November 2002

Final protocol: 22 November 2002

Progress report: 28 February 2003

The progress report will address the following areas:

- Whether progress is on schedule;
- Confirmation of external reviewers, including job title and institution;
- Confirmation of date of receipt of industry submissions (or notification if still outstanding);
- Indication of whether the extent of industry submission data marked 'in confidence' is unreasonable, for example if the whole of the submission is marked 'in confidence';
- Optional opportunity to comment on any problems encountered in producing the report.

Assessment Report: 14 May 2003

G.2 Competing interests

One of our clinical advisers has indicated a potential competing interest. A completed declaration of competing interests form has been submitted along with this protocol.

G.3 External reviewers

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers' signed copies to NCCHTA. Comments from external reviewers and the Technical Lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

Reference

1. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: OUP; 1997.