



NETSCC, HTA

8th September 2011

1. Project title: Systematic review and modelling of the cost effectiveness of Cardiac Magnetic Resonance (CMR) Imaging compared with current existing testing pathways in ischaemic cardiomyopathy.

2. How the project has changed since the outline proposal was submitted

The project should be re-scoped and focus on one or two specific clinical conditions where it is used in the NHS

The project has been re-scoped to focus on the use of Cardiac Magnetic Resonance (CMR) imaging in the assessment of patients with suspected ischaemic cardiomyopathy, focusing on the use of CMR to assess myocardial viability and its role in selecting patients for revascularisation, either by open surgery or percutaneous coronary intervention. This represents one of the main uses of CMR in the NHS.

The timetable will need to be revised

The project timetable has been reduced slightly to account for the re-focussed project plan, though as a complex project 13 months is felt to be a realistic timeframe to complete the project.

The health economics of the study should be strengthened

A health economist has been added to the team of co-applicants to advise on the health economic aspects of the study, design the survey, and focus on collection of economic data from the literature.

The difficulties of collecting data on costs from the literature should be addressed

A survey will now also be used to obtain information on the use of CMR from major cardiac centres in the UK, and this will help to address some of the difficulties collecting cost data from the literature. This survey questionnaire will help to address the issue of how CMR is used across the UK, capacity issues and potential step costs of setting up or expanding CMR services.

We have also strengthened the research team by including Professor Dudley Pennell and Professor Alex Sutton as co-applicants. Professor Pennell is Director of CMR at the Royal Brompton Hospital. He is an internationally recognised expert in CMR. He will provide expertise on the clinical use of CMR, and has been involved in estimating the use of CMR services across the UK.

Alex Sutton is an expert in data synthesis techniques for diagnostic testing data, and has worked on projects with ScHARR in the past synthesising data to inform the decision analysis modelling for health technology assessment of diagnostic testing technologies.

The team should include an interventionist

An interventional cardiologist Dr Allison Morton has joined the research team to provide expertise as a user of the information from Cardiac MR in decisions about revascularisation.

3. Planned Investigation

Research objectives

We aim to assess the cost effectiveness of imaging testing strategies for patients with or suspected of having ischaemic cardiomyopathy to assess for myocardial viability with particular reference to the impact of CMR in the testing pathways.

Specifically we will:

1. Estimate the diagnostic accuracy of imaging tests and pathways where CMR may be a replacement or additional test in patients being assessed with ischaemic cardiomyopathy with a view to revascularisation.
2. Model imaging pathways and synthesise evidence to estimate the cost effectiveness of these imaging pathways, in terms of incremental cost per Quality Adjusted Life Year (QALY) gained per pathway
3. Identify the optimal imaging pathway for investigating patients with ischaemic cardiomyopathy where CMR may be used, and estimate the impact of CMR in terms of cost effectiveness with reference to the NICE threshold for willingness to pay per QALY gained.[1]
4. Identify the critical areas of uncertainty in these imaging pathways where future research would produce most benefit and recommend specific primary research designs to address them.

Existing research

In the UK it is estimated from age specific incidence rates that there are 38,000 new cases of heart failure in men each year, and about 30,000 in women giving an overall new case incidence of 68,000. This incidence rises steeply in the elderly, and with changing demographics incidence is likely to increase in the next few decades. In terms of prevalence it is estimated that there were 393,000 men over 45 with established heart failure and 314,000 women giving a total prevalence of over 700,000 in 2006.[2] Of these patients, coronary artery disease (CAD) is the major aetiological factor for the left ventricular (LV) systolic dysfunction leading to heart failure.

There is increasing success in treating myocardial infarction (MI) with reduced mortality,[2] but inevitably this means more patients survive with severe morbidity post MI. The prognosis for patients post MI is related to the extent of myocardial necrosis, preserved viability, LV dysfunction and degree of stress induced ischaemia.[3]

Viable myocardium is defined as myocardial segments with reduced function at rest but potentially recoverable either spontaneously (stunned) or with revascularisation when perfusion is reduced (hibernating myocardium).[4]

The clinical challenge is to identify those patients with CAD and heart failure with viable myocardium that has potential to recover if revascularised and ensure these patients are appropriately treated with surgical or catheter based coronary intervention, and that those with non-viable myocardium in the target area for revascularisation are not intervened on unnecessarily.

This is particularly important as patients with this condition, often referred to as ischaemic cardiomyopathy characterised by extensive CAD and diminished LV function, have five year survival rates ranging from 50-60%.[5] Survival decreases as LV ejection fraction decreases, the extent of CAD increases and patient age

increases.[6] The LV dysfunction in patients with ischaemic cardiomyopathy is usually due to either myocardial necrosis and scarring or myocardial hibernation.[5] Recognising the presence of viable and hibernating myocardium allows targeted revascularisation to potentially improve LV function, functional capacity and prognosis, though this may only be relevant for patients with severe LV systolic dysfunction (<35%).[4, 7] So patients post MI who have poor LV function, and symptoms of heart failure (ischaemic cardiomyopathy) should be assessed with viability studies. The treatment options are then medical therapy, revascularisation or heart transplantation. For most patients, however, the choice is between offering medical therapy alone or also revascularisation. Revascularisation procedures are associated with an increased risk of perioperative complications so it is important to select appropriate patients for this intervention.[8] Using PET to detect markers of hibernating myocardium, the prevalence of the phenomenon in patients with severe LV systolic dysfunction has been found in about 55% of patients.[9] Of those revascularised, between 55-60% of patients will show evidence of recovery in function in the hibernating myocardium.[10]

Patients in whom assessment for myocardial viability is to be undertaken will have coronary artery angiography to determine the potential for revascularisation if viability is demonstrated in the appropriate arterial territory by non-invasive imaging. Diffuse severe disease may mean there is no feasible means to achieve revascularisation, and in such cases assessment for viable myocardium is unlikely to be useful.

There are four main imaging methods available to assess for hibernating myocardium: [11-13]

- Positron Emission Tomography (PET) scanning examining the uptake of a number of tracers to assess perfusion and metabolism to demonstrate perfusion-metabolism mismatch; the hallmark of hibernating myocardium. PET offers assessment of anaerobic and aerobic metabolism (including glucose use, fatty acid uptake, and oxygen consumption) Other PET applications include assessment of contractile function, and neuronal activity.
- Single Photon Emission Tomography (SPECT) techniques using Thallium-201, or technetium99m labelled tracers, and in clinical practice these are probably the most commonly used techniques to assess patients for viable myocardium across the NHS.
- Echocardiography: This has commonly involved stress echocardiography, to produce dual response to stress (augmentation followed by reduction of contraction) in an abnormal LV segment as an indication of hibernating myocardium. More recent techniques include myocardial contrast echo and tissue Doppler imaging.
- Cardiovascular Magnetic Resonance (CMR) Imaging: with two main techniques available, dobutamine stress CMR, which is analogous to stress echo imaging, or the more recently described and more widely used delayed enhancement CMR technique, which allows assessment of the distribution of myocardial scar and viable tissue alongside an assessment of regional myocardial function. This may be accompanied by CMR stress perfusion imaging, usually using adenosine as a pharmacological stress agent.

With such a range of techniques available to assess patients with ischaemic cardiomyopathy for viable myocardium, which technique to use is often dictated by local availability of equipment and expertise. It is generally accepted that PET scanning is the most accurate technique, but it is mainly used as a research tool and is not readily available to be used in all patients. In some studies PET is described as the Gold Standard method to assess for myocardial viability, but it is not 100% accurate. Studies to assess accuracy of all imaging techniques to detect viable myocardium have been based on evidence of functional improvement of LV function either globally or in defined segments following surgery, and on this basis the sensitivity and specificity of each imaging technique to predict functional improvement have been calculated.[10, 14, 15]

CMR, particularly delayed enhancement CMR is a relatively new technique to assess patients for viable myocardium.[13] There are a number of papers comparing CMR to other techniques in this clinical area, and a more wide ranging technology assessment of the role of functional CMR in assessing myocardial perfusion performed in Canada. [3, 11-13, 15-18] Because CMR is a relatively new technique it has not been included in earlier reviews of methods to assess for myocardial viability.[10, 14] Also no studies report the cost effectiveness of CMR in this or other clinical areas, which makes decision making concerning provision of CMR services within the NHS difficult.

Most magnetic resonance scanners now being installed within the NHS have the capability to perform CMR for assessment of viability and perfusion in planning revascularisation in patients with ischaemic cardiomyopathy, though capacity issues mean access to scanners and scan time remain problematic. Use of MR scanners to perform CMR results in an opportunity cost to other groups of patients who may benefit from magnetic resonance imaging, or results in a need to provide additional scanners to allow CMR to be performed. As demand for CMR is growing, it is timely to assess whether investigating these patients in this way is cost effective in the NHS.

On a broader front there are other areas within cardiology when CMR is being used because it produces images of high spatial and temporal resolution in multiple planes. It is a safe method involving no radiation exposure that can assess cardiac structure and with cine imaging and flow assessment it can assess ventricular function and volumes, valve function, as well as quantify intra-cardiac shunts. Perfusion imaging can make an assessment of myocardial ischaemia, often alongside viability imaging. In a number of patient groups, notably patients with congenital heart disease, valvular heart disease, and other cardiomyopathies, it complements echocardiography in patient assessment and in these clinical areas its use is likely to expand. This work on ischaemic cardiomyopathy would act as an introduction to a programme of research into the wider uses of CMR and its cost effectiveness in the NHS, and would form a template for further study of how this technology should be introduced and utilised.

Research methods

Design

We plan to undertake a cost effectiveness analysis based on secondary research (systematic review, meta-analysis and decision-analytic modelling) to assess the cost

effectiveness of using CMR in the NHS to assess patients with ischaemic cardiomyopathy.

Systematic review and meta-analysis

The systematic review process will involve a number of reviews that will be interlinked and develop alongside the development of the decision-analysis model:

1. Systematic reviews and meta-analysis using standard methodology will be used to assess the diagnostic accuracy of each element of imaging assessment for patients with ischaemic cardiomyopathy involving the main imaging techniques described.
2. Further reviews will be needed to evaluate diagnostic imaging strategies for patients being investigated for ischaemic cardiomyopathy in terms of process measures (e.g costs for imaging investigations) and patient outcomes.
3. Iterative reviews will be required to estimate key parameters in the decision-analysis model, these will include estimates necessary for the estimation of cost effectiveness within the model: including survival and quality of life after intervention to revascularise patients with ischaemic cardiomyopathy, the natural history of patients not accurately diagnosed and long term costs of care after surgery for the cardiac revascularisation

Search strategy

Relevant studies will be identified through electronic searches of key databases including MEDLINE, EMBASE, Science Citation Index and Biological Abstracts. Recent published empirical work will be used to identify optimal strategies for prognosis and diagnosis on MEDLINE and EMBASE[19-22]

Search terms will include:

- cardiomyopath\$, isch\$, imaging, Magnetic resonance imaging, cardiac disease, radionuclide imaging, echocardiography, viability assessment, perfusion scanning, PET, SPECT.
- imaging pathway, imaging guideline\$, plus such terms as
 - cohort studies, longitudinal studies, follow-up studies, time factors, long term, sequela\$, prognosis, and
 - diagnostic terms such as specificity and sensitivity, false positive\$, false negative\$, true positive\$, true negative\$.

References will also be located through review of reference lists for relevant articles and through use of citation search facilities through the Web of Knowledge's Science Citation Index and Social Science Citation Index. Existing systematic reviews will be used both to identify relevant studies and to inform subsequent analysis. In addition systematic searches of the Internet using the Copernic meta-search engine will be used to identify unpublished materials and work in progress. Key authors and professional and academic research groups will also be contacted and asked for unpublished material.

Review strategy

The stages of the review for diagnostic cohort studies will include:

1. Accumulation of references, entry and tagging on a Reference Manager database, enabling studies to be retrieved in each of the above categories by either keyword or textword searches.
2. Two reviewers will independently undertake preliminary review to identify any potentially relevant article based on titles, abstracts and subject indexing. All studies identified for inclusion, together with those where a decision on inclusion is not possible from these brief details, will be obtained for more detailed appraisal.
3. Two reviewers will make decisions on the final composition of included studies, assessed from a hard copy of the item. The decisions will be coded and recorded on the Reference Manager database by the Project Manager.
4. Authors will be contacted, if appropriate, to clarify details and obtain missing data
5. The quality of each study will be assessed against recognised criteria.[19, 21, 23, 24]
6. Data extraction will be undertaken independently with discrepancies being discussed by the data extractors. Those that cannot be resolved at this stage will be referred to the rest of the project team.
7. To ensure that new emerging evidence is incorporated in the model parameters searches will be repeated toward the end of the project, and any new evidence evaluated for incorporation into the reviews.

Studies must have these inclusion criteria: studies must have an appropriate reference standard; studies reporting prospective and retrospective results (with series larger than 20 subjects) in which the diagnostic accuracy and validity of each of the selected imaging techniques can be evaluated in patients with chronic coronary artery disease and LV dysfunction who are potential candidates for revascularization; studies that contain accuracy data (sensitivity, specificity, positive and negative predictive values) or sufficient details so that accuracy data can be calculated; studies reporting results that compare the functional outcome of individuals with and without viable myocardium on each of the selected imaging technique with follow-up with or without revascularization. Studies will also be excluded if they report acute ischemic syndromes, are editorials, letters, case reports, and technical reports.

These methods will also be used to identify studies of the management of ischaemic cardiomyopathy and studies reporting data to inform the decision analysis model, but search terms, filters, selection criteria and quality assessments will be adapted to suit the purpose of each literature search.

Data extraction

The following data will be extracted from each study: population characteristics (age, gender, New York Heart Association (NYHA) functional classification of heart failure), characteristics of the imaging technique used (e.g. CMR technique, radionuclide technique used, echocardiographic technique used), definition of each outcome used, methods used to measure outcomes, study quality criteria (such as blinding of the intervention reference standard groups and independence of the reference standard), prevalence of each outcome, the true positive, false positive, false negative and true positive rates for each outcome.

Data synthesis

For each imaging modality, we will estimate the diagnostic performance (together with associated uncertainty) for diagnosing myocardial viability/hibernation.

The model used to analyse the data will depend on characteristics of the data obtained. For example, if diagnostic thresholds can be assumed constant across studies then simple methods of pooling sensitivity and specificity will be used.[25] If there is implicit or explicit evidence that diagnostic thresholds differ between primary studies, then sensitivity and specificity cannot be considered independent and simultaneous modelling will be required.[26] A detailed assessment of heterogeneity will be conducted in all instances. If possible, meta-regression will be used to explore whether heterogeneity can be explained by study population characteristics, the method of implementation of the intervention, the definition of the outcome or the study quality, although the feasibility of this will depend on the number of individual studies identified and the quality of reporting. Where exploration of covariates is not possible, or (unexplained) heterogeneity remains after the incorporation of covariates into the model(s), random effects will be incorporated to allow for such variability in results between studies.

Covariate effects, unexplainable variability and uncertainty in will all be reflected in the results using appropriate meta-analysis approaches developed specifically for evaluating diagnostic testing data.[27] Since the outputs from these analyses will be used in the decision modelling all such sources of variation and uncertainty will be accurately reflected in the decision modelling, using appropriate sensitivity analysis techniques.

Standard meta-analysis methods will be used to combine multiple estimates, where they exist, for other parameters in the decision model.

A combination of Stata and the MetaDISC statistical software will be used for this analysis.[28, 29]

National questionnaire survey

We will undertake a national survey of major CMR imaging centres to identify the main clinical areas where CMR is being used.

For relatively little expense the survey would allow:

1. Identification of how CMR fits into the diagnostic testing strategies for assessing patients with ischaemic cardiomyopathy at different centres in the NHS, which will be subsequently evaluated in the decision-analysis model.
2. Exploration of issues regarding the provision of CMR and future plans for expansion of CMR imaging facilities, in relation to other imaging modalities such as echo and radionuclide imaging. Additionally wider issues of use of CMR in other conditions, that may form the basis for future research into the use of CMR, will be explored.
3. Background information for machine usage, spare capacity and potential step costs with the increased provision of CMR services in the NHS to be gathered.
4. Provide context to our analysis by ensuring the output of the research is relevant to the NHS.

Decision-analysis modelling

We will develop a decision-analysis model to estimate the costs and QALYs accrued by each potential imaging pathway for patients being assessed with ischaemic cardiomyopathy to guide whether they should have revascularisation, including a 'zero imaging' strategy of operating on all patients without investigation, to enable the incremental cost effectiveness of each imaging technique / strategy to be evaluated against this, and then against each other depending on the definition of standard care (often radionuclide SPECT imaging). Each strategy will be applied to a theoretical cohort of patients being considered for revascularisation for ischaemic cardiomyopathy allowing a direct comparison of results. For each strategy, sensitivity and specificity estimates from the literature review will determine the proportion of patients appropriately identified as benefiting from coronary revascularisation and who benefit from the intervention as well as the proportion who would not benefit but who undergo diagnostic testing.

The following costs will be estimated using data from the literature review and national survey, (and, if necessary expert opinion): initial assessment, diagnostic tests (CMR, radionuclide testing, echocardiography), hospital admission, surgical and minimally invasive intervention, long-term health and social care.

Outcomes will be estimated as QALYs accrued following the decision to employ each management strategy. The expected utility associated with outcomes following testing and intervention for ischaemic cardiomyopathy will be taken from previous studies and from the Health Outcomes Data Repository (HODaR). We will search the literature to identify studies reporting outcomes of survival and quality of life for the various treatment options for patients with ischaemic cardiomyopathy.

The time frame for the model will be the lifetime of the patients. Most patients will incur long term costs, but the level of these costs will be influenced by the diagnostic accuracy of assessment prior to intervention, with this influencing the proportion of patients appropriately managed with revascularisation or with medical therapy only. Sensitivity analysis will be used to explore uncertainty in estimates of long-term costs.

We will undertake a literature review to estimate the effects of radiation exposure associated with some of the investigations used (radionuclide imaging). We will then model these data to estimate a QALY loss and/or cost associated with each radiological investigation. This QALY loss and/or cost will then be applied to every patient in the model who receives a radiological investigation.

Analysis will be conducted in accordance with the NICE reference case.[1] Net benefit analysis will be used to identify the most cost-effective option at varying thresholds of willingness to pay.[30] The optimal strategy at the threshold currently used by NICE for decision-making will be presented as the optimal strategy for the NHS. The methodology used in the decision analytic model will be dependent on the data that are available and the number of health states that are necessary to incorporate, with the most appropriate technique selected.

This approach is preferable to that of attempting to manipulate data to fit a pre-specified modelling structure as that would not be as accurate as choosing the method that can best represent the decision problem. The lead modeller has published papers using a wide range of decision methodologies, including discrete event simulation, [31] meta-modelling,[32] transition state modelling,[33] decision tree modelling[34] and infectious disease modelling incorporating herd-immunity[31] and we are confident that whatever modelling methodology is most appropriate will be able to be constructed. If possible, we shall attempt to calibrate the mathematical model with published data during the construction phase.

Probabilistic sensitivity analyses (PSA) will be conducted in order that any interactions and non-linearities within the modelling are properly considered. Jackknife techniques[35] will be conducted to ensure that a sufficient number of PSA runs have been conducted to ensure that the average calculated from all runs for a management strategy is robust. Additionally the uncertainty associated in the actual mean net benefit will be provided using the percentile method in order that the full uncertainty in the results is reported. These analyses will facilitate the calculation of both full and partial expected value of perfect information, and if it is deemed appropriate an evaluation of the expected value of sample information will also be conducted.

The value of information analysis will help us to determine where funders of primary research in this important area (such as HTA) should direct future studies to ensure that recommendations for policy and practice are more robust.

4. Project timetable and milestones

The project will commence on 1st Feb 2011 and complete by 30th Feb 2012 There will be three phases, although development of the model and the reviewing will be an iterative process as each part will be partly driven by the other:

1. Feb to August 2011: Systematic reviews and meta-analysis
2. August 2011 to January 2012: Decision analysis modelling
3. January and February 2012: Writing up and dissemination

We will provide a progress report by September 1st 2011 this will report progress of the systematic reviews and meta-analysis.

5. Expertise

Steven Thomas is a clinical senior lecturer in Cardiovascular Radiology. He has previously collaborated with the Health Economics and Decision Science unit at SchARR on a number of projects, including a HTA funded assessment of carotid stenosis, with collaborators in Edinburgh, and a HTA funded project evaluating diagnostic tests in DVT. He has also been involved in assessment of the cost effectiveness of treatment in AAA for the recent NICE appraisal of EVAR, with the Centre for Health Economics at York. Jonathan Michaels is Professor of Vascular Surgery, and has a wide experience of systematic reviewing and decision science. He has collaborated and led on a number of projects with the Health Economic and Decision Science unit at SchARR, and the Centre for Health Economics at York. He has worked extensively for NICE.

Alan Brennan is the director of Health Economics and Decision Science at SchARR and has led a large number of successful multidisciplinary projects, and has worked

extensively for NCCHTA. Matt Stevenson has a wide experience of different mathematical modelling techniques and has worked extensively for NICE and the NCCHTA. In 2007 he was an invited expert to a NICE workshop to help formulate further the NICE reference case for evaluating the cost effectiveness of diagnostic techniques. In 2009 he was appointed as a NICE appraisal committee member. Sophie Whyte has recently joined SchARR following completion of her PhD in Pure Mathematics. She has been successfully involved in many consultancy projects which has led to her leading a single technology appraisal for NICE

Andrew Booth is Reader in Evidence Based Information Practice at the School of Health and an international expert in evidence based information practice. The Department of Information Resources has extensive experience of supporting evidence synthesis for NCCHTA and NICE. Phil Shackley is a senior lecturer in health economics at SchARR and has considerable experience of applying health economics techniques in a variety of contexts, including survey design and data synthesis from literature reviews.

Dudley Pennell is an internationally recognised expert in CMR, Director of Cardiovascular MR at the Royal Brompton Hospital, London, Professor of Cardiology, Director of the BHF Research Centre (Centre for Advanced MR in Cardiology) Director of Non-invasive Cardiology, and Director of NIHR Biomedical Research Unit at the National Heart and Lung Institute, London. He is on the Editorial Board for a number of Cardiology journals and is Editor in Chief of the Journal of Cardiovascular Magnetic Resonance.

Abdallah Al-Mohammad is a Consultant Cardiologist with particular interests in heart failure and non-invasive imaging, including Echocardiography, Nuclear Medicine and CMR. In 2008 he became clinical advisor to the Guideline Development Group appointed by NICE for the partial update on Chronic Heart Failure Guidance.

Allison Morton is a Consultant Interventional Cardiologist at Sheffield Teaching Hospitals, with an academic contract with the Sheffield BRU. She will provide expertise as a user of the information from Cardiac MR in decisions about revascularisation.

Alex Sutton is a leading expert in meta-analysis with a particular interest in synthesis for decision modelling who has worked on the evaluation of diagnostic data via collaboration on another HTA project with SchARR looking at the management of DVT.

6. Service Users

No service users are involved in this project at the present time.

7. Justification of the support required

The Project Manager will manage the literature searches, supervise quality assessment of selected papers, assist with meta-analysis and cost effectiveness analysis, write reports and disseminate findings. An experienced Project Manager for the duration of the project will be crucial to ensuring the success of this study.

Project Manager, grade 8, 70% for 13 months = £43,893

The Clerical Assistant (to be appointed) will assist with the survey, literature searches, photocopying, preparing papers and data management.

Grade 3 clerical assistant, 50% for 13 months = £11,322

AB (Director of Health Economics and Decision Science) will provide advice and supervision of the Health economics and decision analysis.

Directly allocated 1% for 12 months =£819

PS (Health Economist) will provide health economic expertise and assistance with the health economics data synthesis and survey design.

Directly allocated 3% for 12 months=£2047

MS (Operational Researcher) will supervise the decision analysis modelling and cost effectiveness analysis.

MS, 10% for 12 months = £6,843

SW, Grade 7, 40% for 12 months = £18,183

AS (Statistician) will provide expert assistance for the data synthesis of diagnostic testing data from the review to input into the model.

AS, 2% for 11 months = £2,760

ST (Lead Investigator) will supervise the Project Manager, co-ordinate the project and oversee all project planning, analysis and report writing, as well as provide clinical and imaging expertise.

Directly allocated, 10% for 13 months = £14,486

DP (Cardiologist) will provide expertise on the role of CMR clinically within the NHS, and comment on the structure and content of the model pathways.

DP, 2% for 11 months = £2,562.

AAM (Cardiologist) will provide clinical and imaging expertise throughout the project.

Collaborators cost will be claimed as NIHR NHS support costs

AM (Interventional Cardiologist) will provide expertise on the use of CMR throughout the project.

AM, 4% from within academic contract for 13 months = £4,350

JAM (Vascular surgeon) will provide clinical expertise and expertise on systematic reviewing, modelling and decision science.

Directly allocated, 4% for 12 months = £5,167

Information Officers will undertake literature searches and document retrieval under supervision of AB (Information Resources).

AB, directly allocated, 2% for 12 months = £1,369

AC, Information Officer (systematic reviewing), G7, 10% for 11 months = £4155

Other expenses will include:

Computing equipment, including licences for systematic review and decision analysis software = £1250.

Questionnaire survey, 250 mailings @ £1.60 per mailing = £400

Travel for conference and dissemination purposes: £1200

Interlibrary loans = £1500

Publication costs, 3 x open access articles @ £900 each = £2700

Estates charges = £10,255

Indirect costs = £52,336

Total requested (80% for HEI staff and facilities) £151,460

8. References

1. Guide to the methods of technology appraisal. National Institute of Health and Clinical Excellence, 2008.
2. Allender S, Peto V, Scarborough P, Rayner M. Coronary heart disease statistics. London: BHF; 2008.
3. Miller S, Helber U, Brechtel K, Nagele T, Hahn U, Kramer U, et al. MR imaging at rest early after myocardial infarction: detection of preserved function in regions with evidence for ischemic injury and non-transmural myocardial infarction. *European Radiology* 2003;13(3):498-506.
4. Marwick TH. The viable myocardium: epidemiology, detection, and clinical implications. *Lancet* 1998;351(9105):815-9.
5. Beller GA. Noninvasive assessment of myocardial viability.[comment]. *New England Journal of Medicine* 2000;343(20):1488-90.
6. Bart BA, Shaw LK, McCants CB, Jr., Fortin DF, Lee KL, Califf RM, et al. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *Journal of the American College of Cardiology* 1997;30(4):1002-8.
7. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *Journal of the American College of Cardiology* 2002;39(7):1151-8.
8. Bax JJ, Poldermans D, Elhendy A, Cornel JH, Boersma E, Rambaldi R, et al. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. *Journal of the American College of Cardiology* 1999;34(1):163-9.
9. al-Mohammad A, Mahy IR, Norton MY, Hillis G, Patel JC, Mikecz P, et al. Prevalence of hibernating myocardium in patients with severely impaired ischaemic left ventricles. *Heart* 1998;80(6):559-64.
10. Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Current Problems in Cardiology* 2001;26(2):147-86.
11. Underwood SR, Bax JJ, vom Dahl J, Henein MY, Knuuti J, van Rossum AC, et al. Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology. *European Heart Journal* 2004;25(10):815-36.
12. Tomlinson DR, Becher H, Selvanayagam JB. Assessment of myocardial viability: comparison of echocardiography versus cardiac magnetic resonance imaging in the current era. *Heart, Lung & Circulation* 2008;17(3):173-85.

13. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *New England Journal of Medicine* 2000;343(20):1445-53.
14. Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *Journal of the American College of Cardiology* 1997;30(6):1451-60.
15. Kaandorp TAM, Lamb HJ, van der Wall EE, de Roos A, Bax JJ. Cardiovascular MR to assess myocardial viability in chronic ischaemic LV dysfunction. *Heart* 2005;91(10):1359-65.
16. Medical Advisory Secretariat. Functional cardiac magnetic resonance imaging (MRI) in the assessment of myocardial viability and perfusion: an evidence-based analysis. *Ontario Health Technology Assessment Series* 2003;3 (6).
17. Cowley D, Corabian P, Hailey D. Functional diagnostic imaging in the assessment of myocardial viability. *Alberta Heritage Foundation for Medical Research (AHFMR)* 1999.
18. Schwitter J. Myocardial perfusion. *Journal of Magnetic Resonance Imaging* 2006;24(5):953-63.
19. Westwood ME, Whiting PF, Kleijnen J. How does study quality affect the results of a diagnostic meta-analysis? *BMC Medical Research Methodology* 2005;5(1):20.
20. Whiting P, Harbord R, Kleijnen J. No role for quality scores in systematic reviews of diagnostic accuracy studies. *BMC Medical Research Methodology* 2005;5:19.
21. Whiting P, Rutjes AWS, Dinnes J, Reitsma J, Bossuyt PMM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. *Health Technology Assessment* 2004;8(25) 1-234.
22. Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J. A systematic review finds that diagnostic reviews fail to incorporate quality despite available tools. *Journal of Clinical Epidemiology* 2005;58(1):1-12.
23. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326(7379):41-4.
24. Lijmer JG, Mol BW, Heisterkamp S, Bossel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282(11):1061-6.
25. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. In: *Systematic Reviews in Health Care: Meta-analysis in context*. 2nd Ed ed. London: BMJ Publishing Group; 2001.
26. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007;8(2):239-51.
27. Sutton AJ, Cooper NJ, Goodacre S, Stevenson M. Integration of meta-analysis and economic decision modeling for evaluating diagnostic tests. *Medical Decision Making* 2008;28(5):650-67.
28. 2006 Stata. Stata Corp. Statistical Software: Release 9.0. College Station, TX. Stata Corporation.
29. Zamora J, Muriel A, Abrair V. Meta-DiSc Version Beta (1.0.10): Metanalysis of diagnostic and screening tests. 2004.

30. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics* 2001;10(8):779-87.
31. Stevenson M, Beard S, Finn A, Brennan A. Estimating the potential health gain and cost consequences of introducing a pre-school DTPa pertussis booster into the UK child vaccination schedule. *Vaccine* 2002;20(13-14):1778-86.
32. Stevenson MD, Oakley J, Chilcott JB. Gaussian process modeling in conjunction with individual patient simulation modeling: a case study describing the calculation of cost-effectiveness ratios for the treatment of established osteoporosis. *Medical Decision Making* 2004;24(1):89-100.
33. Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. *Health Technology Assessment* 2006;10(30) 1-182.
34. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, et al. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. *Health Technology Assessment* 2006;10(15):1-168.
35. Inglehart D. Simulating stable stochastic systems. Comparison of ratio estimators. *Naval Res Logist Quart* 1975;22:553-565.