Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis

C McKenna, C McDaid, S Suekarran, N Hawkins, K Claxton, K Light, M Chester, J Cleland, N Woolacott* and M Sculpher

April 2009
DOI: 10.3310/hta13240
How to obtain copies of this and other HTA programme reports
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:
– fax (with credit card or official purchase order)
– post (with credit card or official purchase order or cheque)
– phone during office hours (credit card only).

Additionally the HTA website allows you either to pay securely by credit card or to print out your order and then post or fax it.

Contact details are as follows:
HTA Despatch
Email: orders@hta.ac.uk
c/o Direct Mail Works Ltd
Tel: 02392 492 000
4 Oakwood Business Centre
Fax: 02392 478 555
Downley, HAVANT PO9 2NP, UK
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods
Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?
Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis

C McKenna, C McDaid, S Suekarran, N Hawkins, K Claxton, K Light, M Chester, J Cleland, N Woolacott* and M Sculpher

Centre for Reviews and Dissemination/Centre for Health Economics, Technology Assessment Group, University of York, UK

*Corresponding author

Declared competing interests of authors: none

Published April 2009
DOI: 10.3310/hta13240

This report should be referenced as follows:


Health Technology Assessment is indexed and abstracted in Index Medicus/MEDLINE, Excerpta Medica/EMBASE, Science Citation Index Expanded (SciSearch®) and Current Contents®/Clinical Medicine.
NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 07/62/01. The protocol was agreed in January 2008. The assessment report began editorial review in September 2008 and was accepted for publication in October 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE
Series Editors: Dr Aileen Clarke, Dr Chris Hyde, Dr John Powell, Dr Rob Riemsma and Professor Ken Stein

ISSN 1366-5278

© 2009 Queen’s Printer and Controller of HMSO
This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.
Abstract

Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis

C McKenna, C McDaid, S Suekarran, N Hawkins, K Claxton, K Light, M Chester, J Cleland, N Woolacott* and M Sculpher

Centre for Reviews and Dissemination/Centre for Health Economics, Technology Assessment Group, University of York, UK

*Corresponding author

Objectives: To determine the clinical effectiveness and cost-effectiveness of enhanced external counterpulsation (EECP) compared with usual care and placebo for refractory stable angina and heart failure, and to undertake analyses of the expected value of information to assess the potential value of future research on EECP.

Data sources: Major electronic databases were searched between November 2007 and March 2008.

Review methods: A systematic review of the literature was undertaken and a decision model developed to compare EECP treatment with no treatment in adults with chronic stable angina.

Results: Five studies were included in the review. In the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP), time to greater than or equal to 1-mm ST segment depression (exercise-induced ischaemia) was statistically significantly improved in the EECP group compared with the control group (sham EECP), mean difference (MD) 41 seconds [95% confidence interval (CI) 9.10–73.90]. However, there was no statistically significant difference between the EECP and control groups in the change in exercise duration from baseline to end of treatment, self-reported angina episodes or daily nitroglycerin use, and the clinical significance of the limited benefits was unclear. There was also a lack of data on long-term outcomes. There were more withdrawals in theEECP group than in the control group as a result of adverse events (RR 1.05, 95% CI 0.67–1.66). There were limitations in the generalisability of results of the trial and, again, a lack of data on long-term outcomes. The review of cost-effectiveness evidence found only one unpublished study but demonstrated that the long-term maintenance of quality of life benefits of EECP is central to the estimate of its cost-effectiveness. The incremental cost-effectiveness ratio of EECP was £18,643 for each additional quality-adjusted life-year (QALY), with a probability of being cost-effective of 0.44 and 0.70 at cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained respectively. Results were sensitive to the duration of health-related quality of life (HRQoL) benefits from treatment.
**Conclusions:** The results from a single randomised controlled trial (MUST-EECP) do not provide firm evidence of the clinical effectiveness of EECP in refractory stable angina or in heart failure. High-quality studies are required to investigate the benefits of EECP, whether these outweigh the common adverse effects and its long-term cost-effectiveness in terms of quality of life benefits.
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glossary and list of abbreviations</td>
<td>vii</td>
</tr>
<tr>
<td>Executive summary</td>
<td>ix</td>
</tr>
<tr>
<td><strong>1 Background</strong></td>
<td></td>
</tr>
<tr>
<td>Description of health problem</td>
<td>1</td>
</tr>
<tr>
<td>Description of technology under assessment</td>
<td>1</td>
</tr>
<tr>
<td>Previous systematic reviews</td>
<td>2</td>
</tr>
<tr>
<td>Definition of decision problem</td>
<td>3</td>
</tr>
<tr>
<td><strong>2 Assessment of clinical effectiveness</strong></td>
<td></td>
</tr>
<tr>
<td>Methods for reviewing clinical effectiveness</td>
<td>5</td>
</tr>
<tr>
<td>Results of the review of clinical effectiveness</td>
<td>6</td>
</tr>
<tr>
<td><strong>3 Assessment of cost-effectiveness evidence</strong></td>
<td></td>
</tr>
<tr>
<td>Systematic review of existing cost-effectiveness evidence</td>
<td>15</td>
</tr>
<tr>
<td>Decision model</td>
<td>15</td>
</tr>
<tr>
<td>Value of information analysis: the decision to acquire more evidence</td>
<td>17</td>
</tr>
<tr>
<td><strong>4 Discussion</strong></td>
<td></td>
</tr>
<tr>
<td>Statement of principal findings</td>
<td>39</td>
</tr>
<tr>
<td>Strengths and limitations of the assessment</td>
<td>40</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>43</td>
</tr>
<tr>
<td>Recommendations for research</td>
<td>43</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>45</td>
</tr>
<tr>
<td>References</td>
<td>47</td>
</tr>
<tr>
<td>Appendix 1 Searches</td>
<td>55</td>
</tr>
<tr>
<td>Appendix 2 Excluded studies</td>
<td>59</td>
</tr>
<tr>
<td>Appendix 3 Quality assessment</td>
<td>65</td>
</tr>
<tr>
<td>Appendix 4 Data extraction tables for clinical effectiveness review</td>
<td>67</td>
</tr>
<tr>
<td>Appendix 5 Details of quality assessment for economic studies</td>
<td>83</td>
</tr>
<tr>
<td>Appendix 6 Assumption of linearity in the economic model</td>
<td>85</td>
</tr>
<tr>
<td>Appendix 7 Exercise used to elicit the beliefs of clinical experts</td>
<td>87</td>
</tr>
<tr>
<td>Health Technology Assessment reports published to date</td>
<td>91</td>
</tr>
<tr>
<td>Health Technology Assessment programme</td>
<td>109</td>
</tr>
</tbody>
</table>
## Glossary

### Cardiac ischaemia
Inadequate blood supply to the heart.

### Cardiac rehabilitation
A structured programme, involving the patient and a multidisciplinary health-care team, consisting of exercise training, behavioural change, education and psychological support to facilitate lifestyle changes and prevent further cardiac events.

### Case series
A group of case reports of patients who were given similar treatment. There is no control group involved.

### Controlled clinical trial
A clinical study involving a control group.

### Coronary artery bypass graft
A coronary revascularisation technique to treat coronary artery disease, which uses a blood vessel (called a graft) from the chest, leg or arm to bypass a narrowed or blocked coronary artery.

### Enhanced external counterpulsation
A non-invasive technique used to improve cardiac perfusion.

### Glyceryl trinitrate
A drug that can be used to treat an angina attack or be taken before exercise or exertion in order to help prevent an attack.

### Heart failure
The symptoms that result from the inability of the heart to respond precisely to the physiological demands for increased cardiac output.

### Intention-to-treat analysis
Analysis that compares participants in the groups to which they were originally assigned. This includes all patients, regardless of whether they satisfied the entry criteria, the treatment actually received and subsequent withdrawal or deviation from the protocol.

### Long-acting nitrates
Drugs that prevent angina pain from developing. These have to be taken regularly and are not used for immediate pain relief, as they take time to start working.

### Myocardial infarction
Known as a ‘heart attack’, whereby blood flow to the heart is impaired by a blood clot in a coronary artery. This can lead to damage to the heart tissue unless treated quickly.

### Oedema
Retention of fluid in the body.

### Paraesthesia
A sensation of tingling, burning, prickling, ‘pins and needles’ or numbness in a part of the body or in the skin.

### Peak VO\(_2\)
The maximum capacity of the body to utilise oxygen during incremental exercise.

### Percutaneous coronary intervention
A coronary revascularisation technique used in the treatment of ischaemic heart disease involving widening of the coronary artery using a stent.

### Randomised controlled trial
A trial in which the participants are randomly allocated to the control or treatment groups.

### Refractory stable angina
Angina that persists, despite optimal drug treatment, when all surgical options have been exhausted.
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
</tr>
<tr>
<td>CEAC</td>
<td>cost-effectiveness acceptability curve</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Reviews and Dissemination</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EECP</td>
<td>enhanced external counterpulsation</td>
</tr>
<tr>
<td>ENBS</td>
<td>expected net benefit of sampling</td>
</tr>
<tr>
<td>EVI</td>
<td>expected value of information</td>
</tr>
<tr>
<td>EVPI</td>
<td>expected value of perfect information</td>
</tr>
<tr>
<td>EVPPI</td>
<td>expected value of partial perfect information</td>
</tr>
<tr>
<td>EVSI</td>
<td>expected value of sample information</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IEPR</td>
<td>International EECP Patient Registry</td>
</tr>
<tr>
<td>ITT</td>
<td>intention-to-treat</td>
</tr>
<tr>
<td>IVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MACE</td>
<td>major adverse clinical event</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MUST-EECP</td>
<td>Multicenter Study of Enhanced External Counterpulsation</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NTG</td>
<td>nitroglycerin</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PEECH</td>
<td>Prospective Evaluation of EECP in Congestive Heart Failure</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>QLI</td>
<td>Quality of Life Index</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SCS</td>
<td>spinal cord stimulation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SF-36</td>
<td>36-item Short Form health survey</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>TENS</td>
<td>transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td>VO₂</td>
<td>volume of oxygen uptake</td>
</tr>
</tbody>
</table>

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.
Background

Stable angina is managed primarily through education and lifestyle advice, drug therapy and vascular surgery. Some patients exhibit symptoms that are not optimally controlled with the (apparently) optimal medication and surgical options available (termed refractory angina). Enhanced external counterpulsation (EECP) is a technique that can be used to improve symptoms in chronic stable angina. However, the role of EECP has not yet been well defined; its use in patients with mild heart failure has also been investigated following positive outcomes in patients with both angina and heart failure in two medium-sized multicentre studies.

Objectives

The primary objectives were: (1) to determine the clinical effectiveness and cost-effectiveness of EECP compared with usual care and placebo for refractory stable angina and heart failure; and (2) to undertake analyses of the expected value of information (EVI) to assess the potential value of future research on EECP.

Methods

A systematic review of the evidence of the clinical effectiveness of EECP was performed. Searches were undertaken to identify relevant published and unpublished clinical and cost-effectiveness literature. The website of the main EECP manufacturer, Vasomedical, was also searched. Update searching was conducted in March 2008 on selected databases.

Randomised controlled trials (RCTs), non-RCTs, cohort studies with a contemporaneous control group (i.e. not historical controls) and case–control studies of patients with refractory stable angina or heart failure were included. Usual care (drugs, cardiac rehabilitation, revascularisation) or placebo (sham EECP) were the comparators. The results of the included studies were discussed in a narrative synthesis.

Results

Clinical effectiveness

Five studies were included in the review. There was one RCT – the Multicenter Study of Enhanced External Counterpulsation trial (MUST-EECP) (n = 139) – and three non-randomised controlled studies of EECP for angina (one comparison of two registries and two small comparisons with usual care). For heart failure there was one RCT – the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) study (n = 187).

The MUST-EECP RCT compared angina patients randomised to either EECP or sham EECP. Time to greater than or equal to 1-mm ST segment depression (exercise-induced ischaemia) was statistically significantly improved in the EECP group compared with the control group, mean difference 41 seconds [95% confidence interval (CI) 9.10–73.90]. There was no statistically significant difference between the EECP and control groups in the change in exercise duration from baseline to end of treatment, self-reported angina episodes per day or daily nitroglycerin use, and the clinical significance of the limited benefits was unclear.
There were more withdrawals due to adverse events (AEs) in the EECP group than in the control group, as well as a greater proportion of patients with adverse events [relative risk (RR) 2.13, 95% CI 1.35–3.38]. There were some weaknesses in the internal validity of this trial and limitations in the generalisability of the results because of the substantial exclusion criteria and large proportion of participants with Class I or II disease; patients seen in clinical practice may exhibit angina more severe than this. There was also a lack of data about long-term outcomes.

The three non-randomised studies compared EECP with elective percutaneous coronary intervention (PCI) and usual care. These studies were of poor quality. There was a high risk of selection bias in all three studies; therefore, the results need to be treated with considerable caution. The study comparing an EECP registry with a PCI registry reported similar 1-year all-cause mortality in both groups.

In the PEECH trial, patients with heart failure were randomised to EECP or to usual care (pharmacotherapy only). At 6 months post treatment, the proportion of patients achieving at least a 60-second increase in exercise duration was higher in the EECP group (RR 1.39, 95% CI 0.89–2.16, \( p = 0.016 \) from logistic regression that factored site and baseline), but the proportion with an improvement in peak VO\(_2\) was similar in both groups, mean difference 0.30 (95% CI –0.53 to 1.13). The clinical significance of this is unclear. The proportion of patients in the EECP group with an improvement in New York Heart Association classification was higher at 6 months (RR 2.25, 95% CI 1.25–4.06), as was the mean exercise duration, mean difference 34.6 (95% CI 4.86 to 74.06). For most outcomes, the results at 6 months reflected those at 3 months except for improvement in quality of life with EECP, which was lower at 6 months than at 3-month follow-up. There were more withdrawals in the EECP group than in the control group as a result of AEs (RR 1.05, 95% CI 0.67–1.66). There were some limitations in the generalisability of results of the trial, and the 6-month follow-up period provided limited data on long-term outcomes.

### Cost-effectiveness

The review of cost-effectiveness evidence found only one unpublished cost–utility analysis, which, from a UK NHS perspective, had a number of important limitations. The base-case analysis for a population of patients with angina severity similar to participants in the MUST-EECP trial demonstrates that the long-term maintenance of quality of life benefits of EECP is central to the estimate of cost-effectiveness. If quality of life benefits of EECP are assumed to be maintained for no more than 1 year after treatment, EECP does not appear to be cost-effective, as defined by the National Institute for Health and Clinical Excellence’s cost-effectiveness threshold range (National Institute for Clinical Excellence, 2004). In contrast, if quality of life benefits are maintained over a lifetime, the cost-effectiveness of EECP appears clear, with a resulting incremental cost-effectiveness ratio well below conventional thresholds. The base-case analysis, based on pooled expert beliefs about the durability of quality of life benefits, suggests that EECP is cost-effective (incremental cost-effectiveness ratio = £18,643) for this patient population, but the probability is around 0.5, indicating high uncertainty in the estimate. Value of information analysis suggests that future research in this area is likely to be of significant value.

### Conclusions

The results from a single RCT do not provide firm evidence of the clinical effectiveness of EECP in refractory stable angina. Further, higher quality RCTs are required to investigate the benefit of EECP in terms of time to ST segment depression, exercise duration, angina frequency and patients’ requirements for nitroglycerin, and whether these outweigh the common adverse effects associated with this intervention.

Similarly, the results from a single RCT in heart failure do not provide firm evidence of the clinical effectiveness of EECP. Statistically significant modest benefits were seen in terms of exercise duration and New York Heart Association classification; however, their clinical significance is unclear. These effects need to be investigated in further RCTs.

To date, the impact of EECP on mortality or major adverse cardiovascular events has not been investigated in angina or heart failure.

EECP is cost-effective if the observed quality of life benefits are assumed to continue throughout a patient’s lifetime. However, there remain uncertainties around the longer-term effects of the intervention.
**Suggested research priorities**

In order to draw firmer conclusions regarding the effectiveness of EECP, further RCTs in both angina and heart failure are warranted. For angina, the value of information analysis suggests that future research in this area is likely to be of significant value. This research should be directed towards obtaining more precise estimates of the quality of life following EECP treatment and the duration over which these benefits are expected to be maintained.

Long-term follow-up trials assessing quality of life from EECP in both refractory stable angina and heart failure are required. There is also an important need to establish the efficacy of EECP in patients with truly refractory severe angina, who have much more severe symptoms than patients in the MUST-EECP study. The design of any future trial should take account of existing angina guidelines, such as SIGN 2007 (Scottish Intercollegiate Guidelines Network, 2007), and ensure correct selection of patients for EECP therapy, i.e. only after education, comprehensive rehabilitation and real optimisation of medication. The investigation of adverse effects should be an important outcome in any future RCT.
Description of health problem

Stable angina

Angina is the term used to describe symptoms that indicate inadequate perfusion of the heart (ischaemia), and it is characterised by discomfort in the chest, shoulder, back, arm or jaw. Angina symptoms are highly subjective and there is little correlation between these and the extent of cardiac ischaemia. This condition is most commonly caused by coronary artery atherosclerotic disease, whereby atherosclerotic plaques impede blood flow to the heart. Risk factors include hypertension, overweight and elevated serum cholesterol levels. Other less common causes of angina include valvular heart disease, uncontrolled hypertension and endothelial dysfunction not associated with atherosclerosis. The severity of angina can be indicated using the Canadian Cardiovascular Society (CCS) class scale. There are three types of angina: stable, unstable or variant.

There are approximately 95,000 new cases of angina in the UK each year, around 52,000 cases in men and 43,000 in women, with an estimated 5% of men and 3% of women aged 35 and over having experienced angina. Estimates for 65- to 74-year-olds are 6–16% of men and 3–10% of women. The studies on which these figures are based did not distinguish between the different types of angina. It has been estimated that in 2000 the cost of National Health Service (NHS) health care that could be directly attributed to angina was £669 million, and the largest proportion of this cost was hospital admission, particularly in relation to revascularisation procedures.

Stable angina is defined as angina symptoms that have followed a predictable pattern over 2 months. This type of angina is triggered by activities that increase oxygen demand, such as exercise, stress, cold weather and eating. The pain is usually relieved by rest or medication.

Stable angina is managed primarily through education and lifestyle advice, drug therapy and vascular surgery. Glyceryl trinitrate is used for immediate relief and prevention of angina symptoms before exertion. Beta-blockers, calcium channel blockers, potassium channel activators and long-acting nitrates are used singly or in combination to alleviate angina symptoms in the long term. As patients with angina due to coronary heart disease (CHD) have an increased risk of cardiovascular disease (CVD) events, they may also receive preventative drug treatment such as antiplatelet therapy, lipid lowering therapy and angiotensin converting enzyme (ACE) inhibitors. Additionally, coronary revascularisation may be used to relieve symptoms in selected high risk patients with particular coronary anatomy, but may not necessarily improve mortality compared with medical management. The techniques currently used are percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

A number of patients exhibit angina that is not ideally controlled with the (apparently) optimal dose of medication and has also exhausted all coronary revascularisation options. This is termed refractory stable angina; the numbers of those affected by it are unknown; however, a Swedish investigation carried out in 1998 suggested that 5–15% of patients referred for coronary angiography may have had refractory stable angina. Although some studies have shown that symptoms of angina that initially seems refractory are improved by optimising drug regimens, some patients remain incapacitated by their angina pain.

The Scottish Intercollegiate Guidelines Network (SIGN) guidelines for management of refractory angina recommend that, initially, rehabilitative, educational and cognitive behavioural methods should be employed. Other therapeutic options which could then be considered include spinal cord stimulation (SCS), transcutaneous electrical nerve stimulation (TENS), left stellate ganglion blockade, endoscopic thorascopic sympathectomy, angiogenesis, opioids and surgical transmyocardial revascularisation, although there is little evidence of the effectiveness of these methods.

Heart failure

Heart failure is symptomatic of the inability of the heart to precisely respond to the physiological demands for increased cardiac output. It may arise
through a cardiac or non-cardiac disorder. The most common cause of heart failure is myocardial dysfunction, most frequently the type in which left ventricular contraction is reduced. The majority of cases are due to CHD, usually with a history of myocardial infarction. Other cases are due to non-ischaemic cardiomyopathy, which has a variety of causes such as hypertension, alcohol excess and idiopathic dilated cardiomyopathy. A classification system for the severity of heart failure has been produced by the New York Heart Association (NYHA).9,10

Heart failure can be chronic or acute. Chronic heart failure is characterised by symptoms such as exertional breathlessness and fatigue, signs of fluid retention and signs of any underlying cardiac disorder. The term acute heart failure is mainly used to describe acute (cardiogenic) dyspnoea and signs of pulmonary congestion including pulmonary oedema. Data from the Heart of England Screening Study suggest that more than 3% of people in the UK aged 45 years and over have definite or probable heart failure,4 and the Hillingdon Heart Failure Study estimated that approximately 40% of people die within 1 year of initial diagnosis.11 Heart failure has been shown to have a detrimental effect on quality of life (QoL) when compared with the general population.12 The areas most affected were physical function, role limitation due to physical function, social functioning, energy and health perception.12

In order to prevent the progression of heart failure, a number of pharmacological therapies are used. The main classes of these are ACE inhibitors, beta-blockers, angiotension receptor blockers, aldosterone antagonists, diuretics, loop diuretics with metolazone, and digoxin. Patients with chronic heart failure often have underlying CVD and commonly have other conditions, such as renal impairment or angina, for which they receive additional treatment.9

Description of technology under assessment

Enhanced external counterpulsation (EECP) is a device that can be used in stable angina to relieve angina symptoms. Although it is widely used in North America, use of this technique in Europe is limited.8 To date, it has been utilised in chronic stable angina patients who are not suitable for coronary revascularisation or those who have chosen not to undergo revascularisation.6,13 If effective, EECP may offer a therapeutic alternative that does not involve the risks carried by surgery. However, the role of EECP has not yet been well defined.13 Despite heart failure previously being a contraindication for EECP, the use of EECP in mild heart failure has recently been investigated following positive outcomes in patients with both angina and heart failure in two small studies.14 EECP is a non-invasive device in which three paired pressure cuffs are wrapped around the patient’s calves, lower thighs and upper thighs, and are inflated in this order during diastole. These cuffs deflate simultaneously at the onset of systole, thus releasing the pressure. Coronary perfusion pressure is improved through diastolic augmentation, which improves afterload reduction, and increased venous return, which in turn increases cardiac output. The release of pressure during systole also decreases peripheral vascular resistance, thereby enhancing systolic unloading and decreasing cardiac workload. Throughout this process, the patient is connected to an electrocardiogram (ECG) monitor and a finger plethysmograph, to measure changes in arterial blood flow. The R wave of the ECG is used as the trigger for inflation and deflation. The course of treatment typically involves 35 sessions each lasting 1 hour over a 7-week period.13 The timing between EECP sessions can vary in clinical practice, depending on patient preference and tolerance for the therapy. This treatment regimen has been developed empirically, and alternatives have not yet been investigated. There appear to be few adverse effects associated with this treatment but those reported are related to the equipment used, i.e. leg and back pain, abrasion of skin, bruising, blistering, oedema and paraesthesia.13

Previous systematic reviews

A recent review of EECP by the Ontario Ministry of Health and Long-Term Care summarised data derived from two randomised controlled trials (RCTs) and a number of case series and registry data to evaluate the efficacy of EECP for refractory stable angina and heart failure. For angina, a number of outcomes were investigated using data from one RCT, the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial (n = 139), one comparative study with age and gender matched controls (n = 40), nine sets of registry data that varied in size from 249 to 4592 patients and seven case series involving 23–1532 patients. The effects of EECP on heart failure were assessed using data from one RCT, the Prospective
Evaluation of EECP in Congestive Heart Failure (PEECH) trial \( (n = 187) \), four sets of registry data ranging from 127 to 1958 patients and one case series \( (n = 32) \).\(^{14}\)

The RCTs indicated that EECP may be beneficial in both chronic stable angina and heart failure. The other studies (registry data and case series) also suggest that EECP may improve patient outcomes. Angina patients were reported to decrease nitroglycerin use, experience a reduction in angina symptoms and show an improvement in angina class and in QoL. Improved left ventricular ejection fraction (LVEF), NYHA functional class, decreased rate of exacerbation and improved QoL were reported in heart failure patients. However, there were numerous methodological limitations to the registry data and case series, such as lack of comparison group, conclusions based on subjective assessment and lack of completion of the case series study for heart failure. Overall, this review concluded that there was insufficient evidence to support the use of EECP in refractory stable angina CCS III–IV or heart failure. Adverse events (AEs) were also reported in eight studies (five registry studies, \( n = 10,969 \), and three case series, \( n = 2662 \)) for angina and five studies for heart failure (four registry studies, \( n = 3193 \), and one case series, \( n = 32 \)). The AEs reported in studies that investigated EECP for angina included serious cardiac events and major adverse cardiac events (MACEs), musculoskeletal and skin trauma, myocardial infarction (MI), angina, chest pain or silent ischaemia, ECG change, arrhythmia, revascularisation procedures and death. When reported, the AE rate ranged from 3% to 40%. In the studies that investigated EECP for heart failure, the AEs reported included MACEs, death, PCI and incidence of all-cause hospitalisations, and rates ranged from 5% to 72%.\(^{14}\)

The search end date for this review was March 2006. It was unclear how extensive the searches were, as the search strategy was not available. Also, only English language articles were included, and it was unclear whether unpublished studies were sought. Therefore, we conducted new searches for evidence rather than update this earlier review.

**Definition of decision problem**

There is a question regarding whether EECP should be a more widely available therapy within the NHS and whether further research should be conducted in order to help in the making of that decision. This report presents our technology assessment of EECP for stable angina and heart failure. The primary objectives were (1) to determine the clinical effectiveness and cost-effectiveness of EECP compared with usual care and placebo for chronic stable angina and heart failure and (2) to undertake analyses of the expected value of information (EVI) to assess the potential value of future research on EECP.
Methods for reviewing clinical effectiveness

The systematic review of the evidence for clinical effectiveness was undertaken following the general principles recommended in the Centre for Reviews and Dissemination (CRD) Report 4.15

Search strategy

Searches were undertaken during November and December 2007 to identify published and unpublished relevant clinical and cost-effectiveness literature. MEDLINE, MEDLINE In-process, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, CENTRAL, DARE and Inside Conferences were searched. The National Research Register, ClinicalTrials.gov, Current Controlled Trials Meta Register and the US Food and Drug Administration website were searched as well as the website of the main EECP manufacturer, Vasomedical. The searches were limited to material produced since 1980. No language or geographical restrictions were applied. Update searching was conducted in March 2008 on selected databases. Full details of the search strategies are reported in Appendix 1. In addition, the main manufacturer was contacted for relevant information.

Titles and abstracts were examined for relevance by two researchers, and all potentially relevant papers were ordered. Full papers were independently examined for relevance by two researchers based on the inclusion criteria below. Disagreements were resolved by consensus.

Inclusion and exclusion criteria

Studies were included in the review if they met the following criteria:

- **Population** Patients with chronic stable angina or heart failure.
- **Intervention** EECP using the prescribed dose of 35 hours of treatment over a continuous period without significant breaks (usually once or twice daily over 4–7 weeks).
- **Comparator treatment** Usual care (drugs, cardiac rehabilitation, revascularisation) or placebo (sham EECP). Dose comparison trials were also eligible, if available.
- **Outcomes** Mortality due to CHD, all-cause mortality, and morbidity measures such as hospitalisation, change in angina severity classification (CCS classification), change in heart failure severity classification (NYHA classification), diuretic dose (in heart failure), exercise duration on treadmill, time to 1-minute ST segment depression, peak oxygen consumption [volume of oxygen uptake (VO₂)] and health-related quality of life (HRQoL).
- **Study design** Randomised controlled trials were eligible for inclusion. It was anticipated that very few randomised studies would be available; therefore, the following study designs were also included: non-randomised controlled trials, cohort studies with a contemporaneous control group (i.e. not historical controls) and case-control studies. Studies without a control group, such as case series, were not included. Reports published as meeting abstracts were also excluded when insufficient methodological details were reported to allow critical appraisal of study quality and this information could not be obtained from the authors.

Data extraction

The data extracted included patient characteristics (age, sex, baseline disease severity, comorbidities), details of intervention and comparator, adherence, length of follow-up and study quality (see below). Authors of the included RCTs were contacted for further information but this was not available.

Data were extracted by one researcher using a standardised data extraction form in Evidence for Policy and Practice Information (EPPI)-Reviewer, and were checked by a second. Discrepancies were resolved by discussion, and, if necessary, a third opinion was sought.

Study quality

The quality of studies of clinical effects were assessed based on criteria specific to the different included study designs using criteria and guidance from CRD Report 415 and Deeks et al.16 The
criteria assessed were method of randomisation, allocation concealment, how participants were allocated in non-randomised studies, similarity at baseline, blinding of outcome assessment and use of intention-to-treat (ITT) analysis (see Appendix 3 for a full list of criteria).

**Methods of analysis/synthesis**

Key study characteristics, patient outcomes and study quality were summarised in narrative and tables. Given the limited number of studies available, the diversity of study designs, patient characteristics and outcomes assessed, it was not feasible or appropriate to pool the studies statistically. The results of studies were therefore discussed in a narrative synthesis.

**Results of the review of clinical effectiveness**

**Quantity and quality of research available**

The literature searches identified 327 potentially relevant references. Titles and abstracts were screened in duplicate, and 167 full papers were ordered for further assessment (Figure 1). At the full-paper screening stage, 157 papers were excluded. Sixty-nine of these were excluded because they were reports of case series or EECP registries and did not have a control group (see Appendix 2 for a list of these excluded papers).

Five studies reported in 10 papers met the review inclusion criteria.

**Study characteristics**

The included studies consisted of one RCT,17 three non-RCTs of EECP for chronic stable angina18–20 and one multicentre RCT of EECP for heart failure21 (Table 1). Both randomised controlled trials (MUST-EECP and PEECH)17,21 and a further study19 reported receiving sponsorship from Vasomedical, the EECP manufacturer. As a result of the variation in study design, clinical characteristics and outcomes assessed, it was not feasible or appropriate to pool the studies statistically. The studies are discussed below in a narrative synthesis grouped by clinical condition and then study design.

**Results of studies of enhanced external counterpulsation for stable angina**

**Randomised controlled trial**

**Study characteristics and quality**

The objective of the MUST-EECP trial conducted by Arora et al.17 was to assess the safety and efficacy of EECP in patients with chronic stable angina. Participants were randomised to EECP of 35 1-hour sessions at a pressure of 300 mmHg, or sham EECP. Sham EECP was similar to EECP, with the exception that suboptimal pressure of 75 mmHg was used. This was described.
by the authors as insufficient to alter patient blood pressure, but sufficient to preserve the appearance and feel of EECP treatment. Only patients with a CCS classification between I and III, documented evidence of coronary artery disease and an exercise treadmill test positive for ischaemia were eligible for inclusion. There was no requirement that patients should be refractory to standard antianginal medication. In addition to excluding patients with class IV angina, patients with overt congestive heart failure or unstable angina, or who had experienced a myocardial infarction or undergone coronary artery bypass grafting in the previous 3 months were excluded. Further exclusion criteria were also applied (see data extraction tables, Appendix 4). The trial population ($n = 139$) was predominantly male (87%) and Caucasian (76%) with a mean age of 63 years. Patients were of CCS classification class I (26%); class II (50%); and class III (23%). Most patients were being treated with nitrates (80%). Other antianginals were calcium channel blockers (58%) and beta-blockers (74%). Aspirin was taken as an antithrombotic by 89% of patients. Further details are given in Appendix 4.

Several outcomes were assessed related to exercise duration, QoL and medication use (see Table 2). Assessments were at baseline and followed the completion of the 35 EECP sessions. The study was powered (80%) to detect a 45-second difference in exercise duration between the groups, based on a between-patient standard deviation of 87 seconds, and using a two-sided test with 0.05 level of significance. QoL was assessed in a 12-month follow-up study using the 36-item short form health survey (SF-36) and the Quality of Life Index (QLI), Cardiac Version III.22 Participants in the original study were given the HRQoL questionnaires at the end of treatment to complete at their convenience and return by mail. Twelve months after completion of treatment, participants in the original study were mailed the HRQoL questionnaires for completion. Follow-up

### TABLE I Details of included studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>Stable angina</th>
<th>Non-randomised controlled studies</th>
<th>Heart failure</th>
<th>Randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Sham-EECP</td>
<td>Usual care</td>
<td>PCI</td>
<td>Usual care</td>
</tr>
<tr>
<td>Number of participants</td>
<td>EECP 72</td>
<td>EECP 15</td>
<td>EECP 323</td>
<td>EECP 20</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>Control 67</td>
<td>Control 10</td>
<td>Control 448</td>
<td>Control 20</td>
</tr>
<tr>
<td>Quality assessmenta</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Randomised</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Participant blind</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Outcome assessment blind</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ITT analysis</td>
<td>Partialb</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

a Full details of quality assessment are reported in Appendix 3. 
b ITT analysis for some outcomes only.
Assessment of clinical effectiveness

Summary details of the quality assessment of this study are reported in Table 1, and the full quality assessment is available in Appendix 3 (based on the main study). The MUST-EECP trial was a seven-centre, double-blind RCT. Treatment allocation was administered centrally and allocation was concealed. The intervention and control group were not balanced at baseline for duration of angina and a higher proportion of previous MI. The study was designed to blind participants and investigators processing and collecting data; it was not possible to blind those administering the treatment. Although ITT analyses (excluding two patients who withdrew prior to first treatment) were reported, this was not reported for all outcomes; ITT was not reported for time to ST segment depression and exercise duration, which was the outcome that the trial was powered to detect. There is therefore the possibility that the treatment effect was overestimated for these outcomes, given the greater number of patients who dropped out from the EECP arm (18%) than left the control group (3%).

In addition to some weaknesses in the internal validity of the trial, there are also limitations on the generalisability of the results of the trial. The substantial exclusion criteria and the large proportion of participants with class I or II disease limit the extent to which the findings can be generalised to all patients with refractory stable angina. The patient population included in the MUST-EECP trial may not have exhibited angina that is as severe as that found in some patients referred for EECP in the UK. There was also a lack of data on long-term outcomes and on the impact of EECP on cardiac-related mortality.

Results

The mean change scores for EECP and control for the clinical outcomes are summarised in Table 2. Details of how the outcomes were measured and pre- and post-treatment scores are available in Appendix 4. There was a statistically significant difference between EECP and control on one efficacy outcome, time to greater than 1-mm ST segment depression (exercise-induced ischaemia), which showed a benefit with EECP. There was a mean 37-second improvement in time to ST segment depression in the EECP group compared with a 4-second deterioration in the control group, mean difference 41.0 [95% confidence interval (CI) 9.10–73.90]. However, this result is not derived from an ITT analysis, is likely to be subject to attrition bias and may well overestimate the treatment effect. Similarly, the change in exercise duration from baseline to the end of treatment was not based on an ITT analysis but, even so, the improvement in the EECP group failed to reach statistical significance (Table 2). Also the mean difference, –16.0 seconds (95% CI –47.79 to 15.79), did not reach the level of clinical significance stipulated in the sample size calculation (45 seconds). Small mean reductions between EECP and control in the change in self-reported angina episodes/day or daily nitroglycerin (NTG) use were reported (based on ITT analysis), but they did not reach statistical significance.

There was a further analysis in which patients were categorised based on the proportion achieving a 25% or 50% improvement or worsening of angina frequency (see Appendix 4). There was a statistically significant benefit with EECP compared with control on this outcome; however, given the large number of cells with low values, the method of analysis used was not appropriate.

For QoL, the authors identified four primary outcomes for the analysis: the physical functioning, bodily pain and social functioning subscales of the SF-36, and the QLI score.22 At 12 months, the EECP group reported a greater (statistically significant) improvement than the control group on all of these outcomes except physical functioning (see Appendix 4). However, follow-up data were available from only 71 of the 139 patients enrolled onto the study; therefore, there is a high risk that this sample is not representative of the total study population.

Adverse events

Adverse events were reported up to the end of treatment. There were more withdrawals due to AEs in the EECP group than in the control group, as well as a greater proportion of patients with AEs, device and non-device related (see Table 2). Adverse events classified as device related in the EECP group were paraesthesia (n = 2); oedema or swelling (n = 2); skin abrasion, bruise or blister (n = 13); and leg or back pain (n = 20). A small number of patients receiving sham EECP reported paraesthesia (n = 1); skin abrasion, bruise or blister (n = 2); and pain in the legs or back (n = 7). Leg discomfort was reported in 11.6% of EECP sessions and 4.9% of sham EECP sessions.
TABLE 2 Results of MUST-EECP trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EECP</th>
<th>Control</th>
<th>p-value (between groups)</th>
<th>Between group mean difference (MD)/relative risk (RR) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers randomised</td>
<td>72</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers treated</td>
<td>71</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers withdrawn</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise duration (seconds): mean change (SE)</td>
<td>n = 57</td>
<td>n = 58</td>
<td>p &gt; 0.31b</td>
<td>MD –16.00 (–47.79 to 15.79)</td>
</tr>
<tr>
<td>Time to ≥ 1-mm ST segment depression (seconds): mean change (SE)</td>
<td>n = 56</td>
<td>n = 56</td>
<td>p = 0.01a</td>
<td>MD 41.00 (9.10–73.90)</td>
</tr>
<tr>
<td>Angina episodes/day: mean change (SE)</td>
<td>n = 71</td>
<td>n = 66</td>
<td>p &lt; 0.09c</td>
<td>MD –0.24 (–0.84 to 0.36)</td>
</tr>
<tr>
<td>NTG use/day: mean change (SE)</td>
<td>n = 71</td>
<td>n = 66</td>
<td>p &gt; 0.1d</td>
<td>MD –0.22 (–0.55 to 0.11)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>n = 71</td>
<td>n = 66</td>
<td>p &lt; 0.001</td>
<td>RR 2.13 (1.35–3.38)</td>
</tr>
<tr>
<td>Patients with AE, n</td>
<td>39</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to AE, n</td>
<td>9</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device-related AE, n</td>
<td>37</td>
<td>10</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Non-device-related AE, n</td>
<td>33</td>
<td>15</td>
<td>p &lt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

a Calculated from study data available.
b Treatment group was the main effect and treatment site was the blocking factor.
c Means adjusted for treatment centre.
d Stratified by treatment centre.

In terms of AEs defined as non-device related, nine patients receiving EECP experienced atrioventricular arrhythmia compared with three in the control group, and seven experienced other chest pain compared with three in the control group. Other non-device-related AEs were viral syndrome (EECP n = 1, control n = 0); anxiety (2, 0); dizziness (3, 1); tinnitus (1, 0); gastrointestinal disturbances (1, 1); headache (1, 0); blood pressure change (1, 1); epistaxis (2, 0); angina (1, 1); heart rate change (0, 3); and respiratory (4, 2).

Non-randomised controlled studies

Study characteristics and quality

The three non-randomised studies compared EECP, one with elective PCI and two with usual care (see Table 1).18,20 There was a high risk of selection bias in all three studies. Without random allocation, there was a high risk of unknown systematic differences between patients in the EECP and control groups that may have influenced each group’s prognosis or responsiveness to treatment. In addition, given the nature of the comparators, blinding was not possible, which is particularly problematic given the subjective nature of most of the outcomes.

Results

One study was a comparison of two registries (n = 771), one for EECP and one for PCI. In this study, there were considerable differences between the two groups at baseline, with the EECP group having a higher prevalence of several risk factors.19 One-year all-cause mortality was similar in both groups (Table 3). Fewer patients reported no angina symptoms in the EECP group than in the control group, and the proportion with a CCS classification of III or IV was higher at follow-up (see Table 3). Also, at 1 year a greater proportion of EECP than PCI recipients reported use of calcium channel blockers, long-acting nitrates, angiotensin-receptor blockers and NTG (see Appendix 4). Given the
TABLE 3 Results from non-randomised trials of EECP for stable angina

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment</th>
<th>Control</th>
<th>p-value (between groups)</th>
<th>Between group relative risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holubkov, 2002&lt;sup&gt;19&lt;/sup&gt;</td>
<td>EECP (n = 251)</td>
<td>PCI (n = 422)</td>
<td>NS</td>
<td>0.59 (0.51–0.69)</td>
</tr>
<tr>
<td>1-year all-cause mortality</td>
<td>1.3% (95% CI 0.5–3.5)</td>
<td>3.2% (95% CI 1.9–5.4)</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>No angina symptoms</td>
<td>43.7%</td>
<td>73.4%</td>
<td>p = 0.59</td>
<td>1.64 (1.09–2.48)</td>
</tr>
<tr>
<td>CCS classification III or IV/unstable angina</td>
<td>15.5%</td>
<td>9.5%</td>
<td>p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Barsheshet, 2008&lt;sup&gt;18&lt;/sup&gt;</td>
<td>EECP (n = 15)</td>
<td>Usual care (n = 10)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>CCS classification: median (interquartile range)</td>
<td>Baseline 3.0 (3.0–4.0)</td>
<td>Baseline 3.0 (2.5–4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up 2.0 (2.0–3.0)</td>
<td>p &lt; 0.001</td>
<td>Follow-up 3.0 (2.0–3.5)</td>
<td>p = 0.50</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shechter, 2003&lt;sup&gt;20&lt;/sup&gt;</td>
<td>EECP (n = 20)</td>
<td>Usual care (n = 20)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>CCS classification: mean (SE)</td>
<td>Baseline 3.5 (0.5)</td>
<td>Baseline 3.3 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up 1.9 (0.3)</td>
<td>p &lt; 0.0001</td>
<td>Follow-up 3.5 (0.5)</td>
<td>p = 0.89</td>
<td></td>
</tr>
<tr>
<td>NTG/day: mean (SE)</td>
<td>Baseline 4.2 (2.7)</td>
<td>Baseline 4.5 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up 0.4 (0.5)</td>
<td>p &lt; 0.001</td>
<td>Follow-up 4.4 (2.6)</td>
<td>p = 0.87</td>
<td></td>
</tr>
</tbody>
</table>

NS, not significant.

* Calculated from study data available.

There were limitations in the quality of these studies, as they were performed in the USA, and thus the results need to be treated with considerable caution.

The RCT included patients with predominantly CCS class I or II stable angina and therefore may not be generalisable to a population of patients refractory to standard therapy who are likely to be offered EECP. The findings in favour of EECP either failed to reach statistical or clinical significance or were subject to attrition bias. There was evidence of a benefit with EECP on QoL 12 months after treatment; however, this was based on just under half of the original sample and should be treated with caution.

In summary, the available clinical study data provide only limited evidence of a clinically significant benefit of EECP in chronic stable angina, and even that may not be generalisable to a treatment refractory population.
Results of studies of EECP for heart failure

Randomised controlled trial

Study characteristics and quality

The objective of the PEECH trial, conducted by Feldman et al., was to assess the benefits of EECP in the treatment of mild to moderate heart failure. Patients were randomised to EECP or usual care (pharmacotherapy only). Prior to randomisation, medical therapy was optimised for all patients in compliance with the practice guidelines of the Heart Failure Society of America. EECP was at a pressure of 300 mmHg (reached within 5 minutes of treatment initiation). Only patients with stable heart failure (secondary to ischaemic heart disease or idiopathic-dilated cardiomyopathy), with LVEF less than 35 and NYHA class I or II were eligible for inclusion. Several exclusion criteria were applied (see data extraction tables, Appendix 4). The trial population was predominantly male (76%) and Caucasian (81%), with an mean age of 63 years. Patients were NYHA classification class II (65%) or class III (35%). Most patients (76%) were being treated with ACE inhibitors. Further details are given in Appendix 4.

Assessments were at baseline, end of treatment and 6-month follow-up, which was the primary time point for the analysis. The primary outcomes were the proportion of participants with at least a 60-second increase in exercise duration and the proportion with at least 1.25-ml/kg/minute increase in peak VO₂. The study was powered (90%) to detect at least a 60-second increase in exercise duration from baseline to 6 months (50% of EECP recipients compared with 20% of control subjects), and a 1.25-ml/kg/minute increase in peak VO₂ in 50% of EECP patients and 30% of control subjects at 0.05 level for both end points, or 0.025 for one.

Summary details of this study are reported in Table 1, and the full quality assessment is available in Appendix 3. The PEECH trial was a multicentre randomised trial with allocation concealment and blinded outcome assessment. Because the comparator was usual care, it was not possible to blind patients or those delivering the intervention. An appropriate ITT analysis was reported for the primary outcomes. The proportion of patients not completing the study was higher for the EECP group (23.7%) than for the control group (13.8%), mainly because of a higher frequency of AEs.

There are some limitations in the generalisability of results of the trial: although follow-up did extend beyond end of treatment, the 6-month follow-up can only provide limited information on the long-term outcomes of EECP in patients with heart failure. The inclusion/exclusion criteria were extensive, and the trial population may not reflect patients that would typically be seen in clinical practice for this therapy. In addition, there was a lack of data on cardiac-related mortality.

Results

Table 4 summarises the outcomes measured at the end points of 1-week, 3-month and 6-month follow-up. The primary end point for analysis was assessment at 6 months. There was a statistically significant difference between EECP and control on one primary outcome but not the other (Table 4). A significantly greater proportion of EECP than usual care recipients had at least a 60-second increase in exercise duration from baseline to 6 months (35% versus 25%, p = 0.016), but the proportion with an improvement in peak VO₂ was similar (23% versus 24%, p = 0.698). These results at 6 months reflected those at 3 months.

The results from the secondary outcomes were also mixed. There was a higher, statistically significant proportion of patients in the EECP group with an improvement in NYHA classification post treatment, 3 months’ and 6 months’ follow-up (RR 2.25, 95% CI 1.25–4.06). However, although there was a statistically significant improvement in QoL with EECP compared with control post treatment and at 3-month follow-up, there was no greater benefit with EECP at 6 months (see Table 4).

Adverse events

There were more withdrawals due to AEs in the EECP group than in the control group (12% versus 3%). In the EECP group withdrawal was due to sciatica, leg pain, arrhythmia, non-Q wave MI not attributed to therapy, worsening heart failure, biventricular pacemaker implantation and worsening lung cancer; in the control group withdrawal was due to death (n = 2) and atrioventricular block (see Appendix 4). The proportion of serious AEs and the number of predefined clinical events of interest were similar in both groups (see Table 4). Serious AEs defined as related to EECP treatment were worsening heart failure (n = 1), pulmonary embolism (n = 1) and deep vein thrombosis (n = 1). A single serious AE of worsening heart failure was defined as related to treatment in the control group. Minor AEs were not reported.
### Assessment of clinical effectiveness

#### TABLE 4 Results of the PEECH trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EECP</th>
<th>Control</th>
<th>p-value (between groups)</th>
<th>Mean difference (MD)/relative risk (RR) and 95% CI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise duration (percentage with at least a 60-second increase in exercise duration from baseline to 6 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.4%</td>
<td>25.3%</td>
<td>p = 0.016&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR 1.39 (0.89–2.16)</td>
</tr>
<tr>
<td><strong>Exercise duration [mean change in exercise duration from baseline(s) (SE)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-week follow-up</td>
<td>n = 77</td>
<td>n = 78</td>
<td>p = 0.010&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MD 31.9 (–1.23 to 65.03)</td>
</tr>
<tr>
<td></td>
<td>26.4 (12.2)</td>
<td>−5.5 (11.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>n = 78</td>
<td>n = 82</td>
<td>p = 0.014&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MD 41.5 (4.72–78.28)</td>
</tr>
<tr>
<td></td>
<td>34.5 (13.9)</td>
<td>−7.0 (12.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month follow-up</td>
<td>n = 79</td>
<td>n = 83</td>
<td>p = 0.013&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MD 34.6 (4.86 to 74.06)</td>
</tr>
<tr>
<td></td>
<td>24.7 (15.2)</td>
<td>−9.9 (13.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NYHA classification (percentage with improvement in classification)</strong></td>
<td>n = 93</td>
<td>n = 94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-week follow-up</td>
<td>33.3%</td>
<td>11.4%</td>
<td>p &lt; 0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR 2.85 (1.52–5.32)</td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>31.6%</td>
<td>12.2%</td>
<td>p &lt; 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR 2.66 (1.42–5.01)</td>
</tr>
<tr>
<td>6-month follow-up</td>
<td>31.3%</td>
<td>14.3%</td>
<td>p &lt; 0.01&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR 2.25 (1.25–4.06)</td>
</tr>
<tr>
<td><strong>Peak VO&lt;sub&gt;2&lt;/sub&gt; (percentage with at least a peak VO&lt;sub&gt;2&lt;/sub&gt; increase of at least 1.25 ml/kg/minute from baseline to 6 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.8%</td>
<td>24.1%</td>
<td>p = 0.698&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR 0.96 (0.57–1.63)</td>
</tr>
<tr>
<td><strong>VO&lt;sub&gt;2&lt;/sub&gt; related [mean change in peak VO&lt;sub&gt;2&lt;/sub&gt; (ml/kg/minute)(SE)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-week follow-up</td>
<td>n = 77</td>
<td>n = 78</td>
<td>p = 0.071&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MD 0.5 (–0.32 to 1.32)</td>
</tr>
<tr>
<td></td>
<td>0.1 (0.3)</td>
<td>−0.4 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>n = 78</td>
<td>n = 82</td>
<td>p = 0.119&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MD 0.60 (–0.22 to 1.42)</td>
</tr>
<tr>
<td></td>
<td>0.2 (0.3)</td>
<td>−0.4 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month follow-up</td>
<td>n = 79</td>
<td>n = 83</td>
<td>p = 0.315&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MD 0.30 (–0.53 to 1.13)</td>
</tr>
<tr>
<td></td>
<td>−0.3 (0.3)</td>
<td>−0.6 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QoL [mean change in QoL score (CIs) using Minnesota Living with Heart Failure Questionnaire]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-week follow-up</td>
<td>−8.8 (–7 to −10.9)</td>
<td>−3.5 (−1.5 to −5)</td>
<td>p = 0.01&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>−7.2 (–4.7 to −9.5)</td>
<td>−2.8 (–1 to −4.6)</td>
<td>p = 0.01&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>6-month follow-up</td>
<td>−3.5 (–1.3 to −6.0)</td>
<td>−2.8 (–0.5 to −4.5)</td>
<td>p = 0.32&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with serious AE, n (%)</td>
<td>27 (30.3)</td>
<td>26 (29.5)</td>
<td>NS</td>
<td>RR 1.05 (0.67–1.66)</td>
</tr>
<tr>
<td>Withdrawal due to AE, n (%)</td>
<td>11 (11.8)</td>
<td>3 (3.2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Number of predefined clinical events</td>
<td>89</td>
<td>88</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS, not stated.

<sup>a</sup> Calculated from study data available.

<sup>b</sup> From logistic regression that factored site and baseline.

<sup>c</sup> Number of patients in analysis unclear, but assumed to be the number of patients reported in each study arm for analytical purposes.

<sup>d</sup> These data have been estimated from a figure; it is unclear whether the measure of variance shown in brackets is a 95% confidence interval, standard deviation or standard error.

<sup>e</sup> From logistic regression with treatment as the main effect.
Summary

A single RCT of EECP for heart failure was identified. As with the chronic stable angina trial, the focus was on improvement in symptoms and exercise duration: cardiac-related mortality was not reported. In this trial of patients with mild to moderate heart failure, there was an improvement with EECP compared with usual care control on all outcome measures at the end of treatment. At 6 months’ follow-up, the benefit of EECP in terms of improved exercise duration and NYHA class had been maintained, but not in terms of peak VO₂ or QoL. The clinical benefit to heart failure patients of a 35-second increase in mean exercise duration and a difference of 10% achieving a minimum 60-second increase in exercise duration is unclear.
Chapter 3
Assessment of cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

Methods
A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included.

The following databases were searched for relevant published literature: Cochrane Controlled Trials Register (CCCTR), EMBASE, Health Economic Evaluations Databases (HEED), MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO and Science Citation Index. Full details of the main search strategy for this review are presented in Appendix 1.

All obtained titles and abstracts were assessed for inclusion. The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond and Jefferson. This information is summarised within the text of the report, alongside a detailed critique of the study and the relevance to the UK NHS.

Results

The systematic literature search identified no studies which met the inclusion criteria for the cost-effectiveness review. No economic evaluations were identified that evaluated EECF treatment in patients with angina or heart failure. However, in some studies identified as part of the clinical effectiveness review, results of a cost–utility analysis of EECF for the treatment of chronic stable angina were reported, but no citation or reference to the study was given. The manufacturer of EECF, Vascomedical, was contacted, and a draft report of the unpublished cost–utility analysis obtained. This report was included as part of the cost-effectiveness review. The following sections provide a detailed critique of the cost-effectiveness evidence from the included study and an assessment of the quality and relevance of the data from the perspective of the UK NHS. A quality assessment checklist is provided in Appendix 5.

Review of manufacturer's study
The manufacturer’s study was ‘Enhanced external counterpulsation for the treatment of patients with chronic stable angina pectoris: a cost–utility analysis’.

Overview
The study was designed to investigate the potential economic impact of EECF. A cost–utility analysis was performed to determine whether improvement in angina functional grades with EECF, as classified by the CCS score, results in favourable economic outcomes. Two alternative treatment strategies were considered for the management of chronic stable angina pectoris in patients who were refractory to medical therapy. The two strategies were (1) EECF plus standard American College of Cardiology (ACC)/American Heart Association (AHA) guideline compliant medical therapy, as recommended by the ACC and the AHA, and (2) standard ACC/AHA guideline compliant therapy alone. The main outcome measure was improvement in angina functional class, which was used as a proxy for establishing the improvement on HRQoL from EECF. Other outcomes were measured in terms of the direct costs of treatment and the costs of MACEs. Outcomes were assessed within a 2-year time horizon.

The study was based on a deterministic, Markov decision analytic model of chronic stable angina, with patients modelled over a period of 2 years and evaluated over a cycle length of 1 year. Using cohort simulation, patients cycled into one of six possible health states: (1) no angina symptoms, (2) CCS class I angina, (3) CCS class II angina, (4) CCS class III angina, (5) CCS class IV angina and (6) death. All patients entered the model after receiving one of the two alternative treatment strategies, and were assigned to one of the health states. Based on the effect of treatment on CCS angina class, the patients advanced into one of four transitional states: (1) better, (2) same, (3) worse and (4) death. These four transitional states
determined whether there was an improvement or a deterioration in angina class. This improvement or deterioration resulted in movement into a health state, with an increment or decrement of one or more grades of the CCS classification. Each health state was assigned an estimate of cost and quality-adjusted survival. The study was conducted from a US payer’s perspective.

**Summary of effectiveness data**

The effectiveness of treatment was based on the assumption that therapies for chronic stable angina should aim to eliminate anginal chest pain and restore functional capacity through improvement in CCS classification angina level. Therefore, the effectiveness of treatment was determined by the available data required to populate the transition probabilities between the various states of the model. Initial Markov state probabilities were based on prevalence data from Michaels \textit{et al.}\textsuperscript{25} and Kandzari \textit{et al.}\textsuperscript{26} for the EECP plus medical therapy treatment and the medical therapy alone groups respectively. Neither of these studies was based on RCT data. Michaels \textit{et al.}\textsuperscript{25} report outcomes in patients receiving EECP plus medical therapy from the International EECP Patient Registry (IEPR). The majority of the patients were reported to have CCS class III (61%) and CCS class IV (26%). The outcome of the cohort receiving medical therapy alone was based on observational data reported in the study by Kandzari \textit{et al.}\textsuperscript{26} The majority of these patients were reported to have CCS class IV (64%) and CCS class III (14%). Both studies were assumed to be representative of the population typically presenting for EECP treatment in the clinical setting.

One- and 2-year transition probabilities were derived from the IEPR for the EECP treatment group, while for the non-EECP group assumptions for the transition probabilities for asymptomatic, CCS class I and class II states were derived from data from the Second Randomised Intervention Treatment of Angina (RITA-2) trial.\textsuperscript{27} Assumptions for the class III and IV transition probabilities for the non-EECP group were based on a weighted means analysis of pooled data from trials on transmyocardial laser revascularisation and percutaneous myocardial laser revascularisation.

**Summary of resource utilisation and cost data**

Costs associated with antianginal treatment and treatment for MACEs were considered. These costs were based on Medicare reimbursement rates, the Medicare Physician Fee Schedule, previously published studies and the Red Book for wholesale drug costs. Codes applicable to procedures and diagnoses were identified through the International Classification of Diseases (ICD-9), Current Procedural Terminology (CPT), Ambulatory Payment Classification (APC), Diagnosis Related Group (DRG) and the Healthcare Common Procedural Coding System (HCPCS). Costs were reported in US dollars for the year 2004 and discounted at an annual rate of 3%. Productivity and personal care costs were not included in the analysis.

The cost of EECP was based on a standard EECP regimen consisting of 35 1-hour treatment sessions. Using an estimated Medicare payment rate of 80%, the cost of EECP was estimated to be $3654 based on utilisation rates of 75% and 25% in the clinic and hospital outpatient settings respectively. Baseline medical therapy was based on pretreatment medication usage patterns reported in Michaels \textit{et al.}\textsuperscript{25} and was assumed to be identical for the two treatment strategies. Medical therapy included beta-blockers ($601 per annum), calcium antagonists ($470 per annum), rescue nitrates ($31 per annum) and long-acting nitrates ($505 per annum). The cost of MACEs was based on the annual probability of having CABG (unit cost $27,316), MI (unit cost $7008), PCI (unit cost $12,055), cardiac-related hospitalisation (unit cost $2786) and visit to an accident and emergency department (unit cost $2231) given treatment received.

**Summary of utility data**

Quality of life for the individual health states was obtained from published studies. Utilities were selected to reflect a general trend of decreasing QoL with increasing angina severity. For asymptomatic chronic stable angina, a utility value of 0.99 was assigned. For the progressive CCS functional classes of angina, utilities of 0.98, 0.90, 0.83 and 0.79 were applied to class I, II, III and IV respectively. A disutility was applied to MI for the duration of the event by subtracting a utility of 0.72 associated with MI from the baseline health state utility. Quality-adjusted life-years (QALYs) were calculated by multiplying the utility weights of each health state by the time in the health state.

**Summary of cost-effectiveness data**

For 66-year-old patients with chronic stable angina, EECP plus standard medical therapy was estimated to be more effective, with an additional benefit of 0.27 QALYs, but more costly, at an incremental cost of $845, than standard medical therapy alone.
over 2 years. The corresponding incremental cost-effectiveness ratio (ICER) was $3126 per additional QALY gained. The gain in QALYs can be attributed to the differences in QoL (in terms of utilities) between the CCS angina level states. The transition probabilities to states of higher CCS level are lower for the EECP plus medical therapy strategy than for standard medical therapy, leading to more favourable outcomes in the former treatment group. The costs between the two groups were similar. The additional upfront cost of EECP was offset by the lower probability of MACEs (with their associated costs) in the EECP plus medical therapy group.

A series of univariate sensitivity analyses were performed over a range of estimates for patients with chronic stable angina. The one-way analyses indicated that the ICER was most sensitive to variations in the transition probabilities associated with CCS class III and IV angina states. Decreasing the probability of improvement in class III angina with EECP plus medical therapy resulted in a substantial change in the relative position of medical therapy alone to EECP plus medical therapy treatment. When the probability of improvement in class III with EECP was less than 0.145, medical therapy alone was marginally more cost-effective.

Discussion

The results of the manufacturer’s analysis suggest that the addition of EECP to standard medical therapy is cost-effective for patients with chronic stable angina based on a cost-effectiveness threshold of at least $5000 per QALY gained. However, the study suffers from a number of major limitations. The use of non-randomised control data to inform the effectiveness estimates has led to reliance on assumptions that have been formulated from multiple sources. The model focuses primarily on the improvement in CCS classification angina level, but the transition probabilities used to represent these improvements are not comparative for the EECP treatment strategy relative to the medical therapy alone strategy. In addition, the link between CCS class level and HRQoL utilities is not well established. A number of assumptions for the utility values have been adopted based on a variety of different sources for each angina grade. The extent to which joint uncertainty in the model parameters has an impact on the overall estimate of cost-effectiveness has not been explored in a sensitivity analysis.

From a UK NHS perspective, the study has a number of additional limitations. The data are mostly sourced from a variety of US studies, and the costs are specific to the US. Consequently, it is difficult to assess the generalisability and transferability of the data to a UK setting, where the pattern of care is likely to be different. In the US, EECP is more developed in terms of its use than in the UK. The following section presents a new decision analytic model that has been developed to provide a more appropriate analysis in the context of the UK NHS.

Decision model

Overview

The review of cost-effectiveness studies in the previous section identified no formerly published studies on the cost-effectiveness of EECP for angina or heart failure. This lack of economic evaluations is largely due to the paucity of published evidence for EECP and the limited number of RCTs comparing EECP with alternative treatment strategies in angina or heart failure. Subject to the data that are available, a new decision analytic model was developed to assess the cost-effectiveness of EECP for angina in the UK NHS. The model provides a framework for the synthesis of available data identified from the clinical effectiveness review and the elicitation of unknown parameters from experts in order to evaluate the potential long-term cost-effectiveness of EECP.

The model was populated subject to the data available from the systematic review of clinical effectiveness. The Results of the review of clinical effectiveness section in Chapter 2 identified only two RCTs comparing EECP with an alternative treatment strategy. One of these RCTs assessed the safety and efficacy of EECP in patients with chronic stable angina, while the other assessed the benefits in patients with mild to moderate heart failure. The primary outcome of the clinical review was improvement in HRQoL from EECP. Consideration was given to all the effectiveness outcomes reported in the RCTs (see Chapter 2, Randomised controlled trial) for inclusion in the cost-effectiveness model. A series of additional searches were undertaken to find evidence to relate intermediate end points reported in the trials, such as improvement in exercise duration, to final health outcomes in terms of QALYs. The lack of substantiated evidence to link these intermediate outcomes with final end points meant that the primary outcome for the
model was QoL improvement as assessed directly in the trials.

The model considers the potential long-term costs and benefits associated with the primary outcome of the review: improvement in QoL from EECP. The model evaluates costs from the perspective of the NHS and Personal Social Services (PSS), expressed in £ sterling at a 2008 price base. Outcomes in the model are expressed in terms of QALYs. Both costs and outcomes are discounted using a 3.5% annual discount rate, in line with current guidelines. All stages of the work were informed by discussion with our clinical advisors to provide feedback on specific aspects of the analysis such as the model structure, data inputs and assumptions.

The model is probabilistic in that input parameters are entered into the model as probability distributions to reflect parameter uncertainty, i.e. uncertainty in the mean estimates. Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their associated uncertainty. The probabilistic analysis also provides a formal approach to quantifying the consequences associated with the uncertainty surrounding the model results, and it can be used to identify priorities for future research. The model was developed in the statistical programming package R.

Given the paucity of published evidence for EECP and the lack of RCTs, the potential value of future research in EECP is assessed. The model is used to undertake analyses of the EVI. Bayesian value of information analyses are used to estimate the expected costs of decision uncertainty predicted by the model, and the maximum value that can be placed on additional research aimed at reducing this uncertainty. This provides an upper bound on the value of a future trial in this area, which provides a necessary but not sufficient condition for establishing whether a trial is likely to provide value for money. In addition to providing a global estimate of the total cost of uncertainty related to all inputs in the model, the EVI is estimated for individual parameters (and groups of parameters) contained in the model. To provide a sufficient condition for further research, the expected net benefit of sampling (ENBS) is calculated. The ENBS for a particular study design is the difference between the expected value of sample information (EVSI) and the costs of sampling. It provides a sufficient condition for deciding if further research is worthwhile. For EECP, the ENBS is calculated to establish whether an additional clinical trial is required, the optimal sample size that should be used in the trial design, the appropriate length of follow-up of the trial and the end points that should be included.

The following sections outline the decision problem, the structure of the model, an overview of the key assumptions and data used to populate the model, and the methodology used to assess the potential value of future research in EECP.

**Treatment strategies and population**

The decision problem addressed by the model relates to the cost-effectiveness of EECP in adults with chronic stable angina. During the review process, consideration was given to extending the model to cover adults with heart failure. However, while the general structure of the model was considered to be generalisable across the different patient groups, the evidence requirements to populate the model in patients with heart failure were difficult to fulfil. Our clinical advice is that EECP is more developed in the UK in patients with angina; therefore, a decision was made to constrain the analysis to stable angina only. However, the model provides a framework to assess the cost-effectiveness and EVI associated with EECP in other patient groups.

The decision model evaluates a strategy of EECP treatment compared with no treatment on the assumption that angina patients would receive EECP treatment over and above standard current clinical practice care. This is consistent with the RCT in angina, MUST-EECP, which compared EECP with inactive EECP (see Chapter 2, Randomised controlled trial for full details). The base-case population in the model relates to the baseline characteristics of the population who entered the MUST-EECP trial (see Appendix 4), under the assumption that this trial population is representative of angina patients typically presenting for EECP in the current clinical setting.

**Model structure**

The model is structured to allow the projection of HRQoL benefits beyond the 1-year trial follow-up period of MUST-EECP, and to simulate the experience of angina patients over their lifetime in terms of risk of cardiovascular events and death. The model is projected over a lifetime time...
horizon, by which time all patients will have been predicted to die. In projecting to the lifetime of patients, assumptions need to be made concerning the duration of treatment in terms of repeat (top-up) procedures and the duration of the effect of treatment in terms of sustaining QoL benefits, reducing major CVD events and death. On the basis that there is no evidence to infer that EECP treatment compared with placebo has a differential impact on the risk of developing CVD events and death, it is assumed that the benefits of EECP are purely palliative. The model incorporates the risk of CVD events and death in order to keep track of the number of patients still alive in the model who could potentially benefit from QoL improvements, but because there is no differential impact on costs and QALYs between the treatment strategies resulting from CVD events, the estimate of cost-effectiveness is not affected by these events. The maximum follow-up time in MUST-EECP was 12 months after treatment. A worst-case scenario is one when the benefits achieved after 12 months of treatment are lost in the second year, at which time all patients are assumed to fall back to baseline QoL, i.e. pre-EECP QoL.

A Markov state transition model, as shown in Figure 2, was developed based on the likelihood of sustaining QoL benefits over time. Three health states were defined as ‘responders’, ‘non-responders’, and ‘dead’. The ‘responders’ state represents patients who sustain QoL benefits from EECP. The ‘non-responders’ state represents patients who lose initial QoL benefits from EECP. The ‘dead’ state incorporates death from both cardiovascular and other causes. In the first year after EECP treatment, patients are assumed to achieve, on average, the QoL benefits reported in the 12-month follow-up of the MUST-EECP trial. Given that patients, on average, achieve these QoL benefits at the end of the first year, patients in the second year either continue to sustain the 1-year QoL benefits and will move to the ‘responders’ state, or will lose the benefits by falling back to baseline QoL and entering the ‘non-responders’ state. Consideration was given to adding an additional state representing partial responders, i.e. those patients who partially sustain QoL benefits, whose QoL is better than at baseline but worse than at 12 months after EECP. However, due to a lack of any evidence to populate this transition or determine the QoL of these patients, it was excluded from the model. In the third and subsequent years, responders to EECP in the previous year will either continue to sustain their QoL benefits or enter the ‘non-responders’ state. The response in each year is dependent on patients receiving repeat top-up procedures as considered appropriate. All patients in the model face a risk of cardiovascular events, which eventually lead to death, and are deemed to be at a competing risk of a non-cardiovascular death.

**FIGURE 2** Structure of the model for EECP.
Key assumptions

The cost-effectiveness of EECP in the NHS will be determined by a number of potential factors. These factors relate to the available clinical evidence base and the generalisability of this evidence to the NHS. A standard 35-hour treatment session of EECP will incur upfront costs, with additional costs of EECP incurred with the need for repeat or top-up procedures. For EECP to be considered cost-effective, it will be important to demonstrate that these additional costs result in potential long-term gains in QoL.

The model makes a number of key assumptions in considering the cost-effectiveness of EECP to the UK NHS, including:

- **Quality of life** Potential QoL gains associated with EECP are examined in relation to a number of factors:
  - improved QoL benefits after treatment
  - the duration for which QoL benefits are likely to be maintained.
- **Risk of cardiovascular events** Patients with angina face an elevated risk of CVD events and death. Treatment with EECP is assumed not to confer any differential effect on the risk of developing CVD events and death relative to no treatment.
- **Costs** In addition to the initial upfront cost of a 35-hour treatment session with EECP, patients can receive repeat top-up procedures that incur additional costs.
- **Generalisability of evidence to the UK** In addition to ensuring that the costs associated with EECP are relevant to the UK, consideration is given to whether the existing RCT evidence can be transferred to a UK setting.

There is significant uncertainty in relation to each of these separate aspects. This uncertainty is largely due to the limited evidence base for EECP in the short- and longer-term. The use of decision analysis provides a number of advantages in exploring these uncertainties in more detail:

1. It provides a framework to model both the short- and the long-term benefits associated with treatment.
2. It makes each of these assumptions explicit and can highlight where the current uncertainties exist.
3. It provides a quantitative approach to combining evidence from separate sources, and the use of probabilistic analysis means that the degree of uncertainty surrounding particular inputs can be reflected.
4. The potential impact of the assumptions on the cost-effectiveness of EECP can be considered.
5. The value of additional research to inform the decision problem can be established.

The following sections provide an overview of the model inputs and the methods used to inform the cost-effectiveness of EECP and the value of further research.

Model inputs

The main parameters in terms of clinical effectiveness, costs and QoL are discussed in detail in the following sections.

Clinical effectiveness:

_Improvement in quality of life_

The clinical effectiveness review identified only one RCT where EECP was compared with inactive EECP for patients with angina. All aspects of clinical effectiveness reported in this trial were considered for inclusion in the cost-effectiveness model, including (1) exercise treadmill duration; (2) time to greater than 1-mm ST segment depression; (3) angina counts; (4) NTG use; and (5) QoL. Despite the use of additional searches (full details of the search strategy are reported in Appendix 1), no substantiated evidence was available to link the four intermediate outcomes to final health outcomes in terms of QALYs. As a result, the primary outcome used in the model was improvement in QoL, as reported in the trial itself. At the end of treatment and at 12 months after the end of treatment, the trial reports improvement in HRQoL from baseline, as assessed by the SF-36 and the cardiac version of the QLI. The SF-36 data were used to obtain a utility improvement from baseline to 1 year after treatment for the model (see Quality of life). This utility improvement was taken as the primary effectiveness outcome measure.

The generalisability of the RCT evidence to the NHS is an important issue. In some respects, the 35-hour EECP treatment sessions can be regarded as standard therapy and so, assuming that the characteristics of UK patients are similar to those of the subjects who entered the MUST-EECP trial, the improvements in QoL can be considered generalisable to the UK. However, the pattern of patient care may differ across centres; for example, patients receiving EECP may inadvertently also be receiving some form of psychological support, which may have a direct impact on their QoL. Given that this pattern of care can also vary across centres in the UK, it seems reasonable to assume...
that the patient characteristics of the MUST-EECP trial entrants are on average similar to UK patients.

**Quality of life**

In order to estimate QALYs, it is necessary to quality-adjust the period of time over which the average patient is alive within the model using an appropriate QoL weight (utility). The MUST-EECP trial reported improvements in QoL from baseline to 12 months following end of treatment across the eight dimensions of the SF-36 scale with both the EECP and the inactive EECP treatment arms.\(^2^2\) The improvements are reported in terms of observed change in scale scores divided by the standard deviation for the scale in the general US population. The standard deviation for each scale was taken from Ware et al.,\(^3^4\) then the standardised scores were converted back to obtain the actual observed changes on each of the eight dimensions. A recently developed algorithm was applied to predict a preference-based European Quality of Life – 5 dimensions (EQ-5D) score using the summary scores of the eight SF-36 dimensions.\(^3^5\) This algorithm provides an approach to estimating utility values associated with changes in the domains of SF-36 reported following EECP and inactive EECP. These were used to estimate the incremental change in utility for EECP relative to no treatment over a 12-month period. To incorporate uncertainty in the estimate of the incremental change in utility in the absence of details of sampling uncertainty in the trial, a beta distribution was applied with a standard error equivalent to half the mean change in utility.\(^3^0\)

**Table 5** reports the utility improvement for EECP relative to no treatment at 1 year. Baseline utility values were taken from age- and sex-dependent population norms for the general UK population and adjusted downwards to reflect the presence of angina in this population.\(^3^6\)

Beyond the 12-month period of MUST-EECP, there is no trial evidence available to examine the degree to which the improvement in QoL benefits is sustained over time. In the absence of suitable trial estimates for the duration of treatment benefits, alternative approaches were considered to inform the duration of QoL benefits over time in the model. A wider set of studies incorporating the experience of patients in the IEPR were examined to provide generic measures of QoL beyond 12 months. However, despite examining all published studies in EECP, the review did not identify a single source that could provide a generic measure of QoL beyond 12 months. Typically, most studies forming part of the IEPR have examined QoL in terms of a five-point rating scale, where QoL is reported as (1) poor, (2) fair, (3) good, (4) very good and (5) excellent, before and after EECP and at 2- or 3-year follow-up. These studies suggest that most patients maintain their benefits from EECP at 2 or 3 years after treatment (Figure 3). However, without a generic measure of QoL, it is not possible to map these scores reliably at follow-up to changes in utility over time. In order to encapsulate the treatment duration in terms of sustained QoL benefits, expert elicitation techniques were employed (see below).

**Probability of sustaining treatment benefits over time: elicitation of expert opinion**

In the first year after treatment, patients in the model were assumed to receive, on average, the 1-year QoL improvement seen in the MUST-EECP trial. The sustained duration of these treatment benefits in subsequent years is unknown. Therefore, elicitation techniques were employed with clinical experts to quantify these unknown parameters.\(^3^9\) These techniques involve asking clinical experts to elicit their beliefs about model parameters with or without some estimate of

<table>
<thead>
<tr>
<th><strong>Parameter</strong></th>
<th><strong>Mean change from baseline to 1 year following end of treatment</strong></th>
<th><strong>Incremental mean change (SE)</strong></th>
<th><strong>Distribution</strong></th>
<th><strong>Source</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Active EECP</strong></td>
<td><strong>Inactive EECP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utility</td>
<td>0.1068</td>
<td>0.0351</td>
<td>0.0717 (0.036)</td>
<td>Beta (α = 3.64, β = 47.13) Arora et al., 2002(^2^2)</td>
</tr>
</tbody>
</table>

\(^a\) Standard error (SE) assumed equivalent to half the mean change in utility.

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
Assessment of cost-effectiveness evidence

uncertainty. A consensus or individual expert approach can be adopted. For the transition probabilities of sustaining QoL benefits over time in the Markov model, expert elicitation was used. An Excel-based exercise was designed to elicit the probability of sustaining the first year QoL benefits in the second year, followed by the third year and so on. The exercise was conducted using the individual expert method, with each expert completing the exercise independently and giving their own belief about the unknown quantities with estimates of uncertainty. One repetitive question was asked throughout the elicitation exercise:

In year X, what proportion of sustained year X-1 patients would you expect to sustain the year 1 quality of life benefits?

Experts were given background information to the exercise explaining the QoL benefits achieved at year 1. The first question of the exercise asked experts to provide the proportion of patients in year 2 who are likely to sustain the average year 1 QoL benefits. Given their response, they were then asked whether they would expect the proportion to be different in subsequent years. If they responded ‘No’, the exercise was complete. If they responded ‘Yes’, they were asked to complete the next question which asked them to determine the proportion of year 2 patients who are likely to sustain the average year 1 QoL benefits in year 3. Given their response to year 3, they were then asked whether they would expect the proportion to be different in subsequent years, and so on with the process repeated. In answering the questions, experts were told to assume that patients undergo any additional repeat procedures (or top-up sessions) as required. Therefore, the responses to all questions were conditional on patients receiving as many top-up sessions as might be considered appropriate. The exercise is presented in Appendix 7.

Elicitation format

The format chosen for each of the questions was a frequency chart. Experts were asked to place 20 crosses on the chart to represent their current belief and uncertainty about that particular question (see Appendix 7). For example, if the expert was completely certain about the answer, he or she would place all 20 crosses in one column of the grid. A distribution of uncertainty for the parameters was derived.

A pilot exercise was initially conducted with one expert to ensure that the questions were clear and interpreted correctly. For the final exercise, seven experts were identified on the basis of their experience and knowledge of EECP treatment in the UK. Five of them completed the exercise.

Elicitation results

Means and standard deviations for the probability of sustaining QoL benefits in each subsequent year are shown in Table 6. The results from each expert were linearly pooled to generate a ‘super’ distribution of values. Each expert was given equal weight, and the pooled result was assumed to be representative of the beliefs of UK clinicians.
**TABLE 6** Mean and standard deviation (SD) of the elicited values for each expert separately, and linearly pooled results across experts

<table>
<thead>
<tr>
<th>Expert</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert 1</td>
<td>0.670 (0.091)</td>
<td>0.600 (0.082)</td>
<td>0.526 (0.088)</td>
</tr>
<tr>
<td>Expert 2</td>
<td>0.807 (0.047)</td>
<td>0.886 (0.052)</td>
<td>0.886 (0.052)</td>
</tr>
<tr>
<td>Expert 3</td>
<td>0.785 (0.039)</td>
<td>0.700 (0.057)</td>
<td>0.675 (0.075)</td>
</tr>
<tr>
<td>Expert 4</td>
<td>0.605 (0.104)</td>
<td>0.605 (0.104)</td>
<td>0.605 (0.104)</td>
</tr>
<tr>
<td>Expert 5</td>
<td>0.908 (0.036)</td>
<td>0.905 (0.035)</td>
<td>0.898 (0.043)</td>
</tr>
<tr>
<td>Pooled result</td>
<td>0.757 (0.126)</td>
<td>0.742 (0.150)</td>
<td>0.719 (0.168)</td>
</tr>
</tbody>
</table>

a Conditional on sustaining benefits in the previous year and receiving top-up procedures as considered appropriate.

The beta distribution was fitted to the linearly pooled data (**Figure 4**) and Monte Carlo simulations drawn from this distribution. In a sensitivity analysis, samples were drawn directly from the empirical data.

**Mortality**

The model separates deaths into those caused by CVD events and other causes of mortality, although no treatment effect from EECP in terms of mortality is modelled. The mortality associated with CVD events was informed by

**FIGURE 4** Pooled distribution of elicited responses from five experts for the probability of sustaining QoL benefits in (a) year 2, (b) year 3 and (c) year 4+, with a beta distribution fitted to the data.
the EUropean trial on Reduction Of cardiac events with Perendopril in stable coronary Artery disease (EUROPA) trial. This trial examined the reduction of cardiac events with perindopril compared with placebo on top of standard background treatment in stable coronary artery disease. In a cost-effectiveness analysis, perindopril was evaluated against usual care using data from the EUROPA trial. As part of this analysis, risk equations were estimated for the risk of a cardiovascular event and death, similar to those presented for the Framingham study. These risk equations facilitate the simulation of fatal and non-fatal events that a cohort of coronary artery disease patients would be expected to experience with and without perindopril. The risk equations based on the EUROPA data were used in the current model to estimate the mortality associated with CVD events, assuming patients are taking perindopril. Baseline variables corresponding to the patient characteristics of the MUST-ECCP trial were used in the risk equations. The output was the number of deaths from CVD causes in each yearly cycle based on the likelihood of a first primary event of CVD death, non-fatal MI or cardiac arrest, and the likelihood of subsequent CVD deaths from non-fatal primary events.

The age-dependent risk of other cause mortality was based on standard UK age- and sex-specific mortality rates. These were adjusted to exclude those deaths recorded with an International Classification of Diseases (ICD) code pertaining to cardiovascular disease (ICD-10 I20–I99). The treatments were assumed not to infer a differential mortality effect.

**Resource use and unit costs**

Resource utilisation and cost data were based on treatment received. Because no additional costs are incurred under a no treatment strategy, the only costs included in the model were those associated with EECP, which relate to the standard 35-hour treatment sessions and the need for repeat top-up procedures over time. The costs were derived from UK sources and expressed in £ sterling at a 2008 price base.

The cost of EECP per patient is based on the average number of patients per annum that a centre can currently handle and the cost of consumables. UK centres currently run at about 12 patients per annum [Ken Miles, Vasogenics (UK) Ltd and Wayne Sheedy, Castle Hill Hospital, Cottingham, personal communication, 2008], but this can be increased to 15 patients in the first few years and up to 20–25 patients per year in subsequent years with increased staffing. An average of 12 patients per year was used in the base-case analysis. The capital cost of a new EECP machine (AngioNew) was estimated to be £90,000 + VAT (including installation and training for three therapists for 5 days). This estimate was based on information provided by Ken Miles (personal communication). The machine is expected to have a useful life of about 10 years, which gives an equivalent annual cost of £10,822 (with an annuity factor for 10 years included at an interest rate of 3.5% per annum). Typical equipment replacement costs include one or two sets of cuffs per year, one set of hoses per year and replacement of the pleth every 2 years. The unit costs associated with each of these were informed by Vasogenics’ current price list (effective from April 2007). The consumables per patient for all 35 sessions are typically one pair of trousers, an ultrasound scan, gel, and ECG electrodes. Table 7 provides a breakdown of the total cost per patient for 35 hours of EECP treatment. Allowing for overheads and staffing costs, the total cost per patient was estimated to be £4347 per treatment over a 35-hour course. Some patients may receive a repeat or top-up procedure involving fewer treatment sessions (for the probability of repeat procedures see Repeat procedures). The cost per session was obtained by dividing the total cost of treatment by 35, giving a cost of £124 per session. The additional cost of repeat procedures was based on an average of 10 additional sessions. In a sensitivity analysis, the total cost of EECP was varied from –£1000 to £1000 to reflect the possibility of increased/decreased utilisation (patient throughput) in some centres.

**Repeat procedures**

A typical course of EECP involves a total of 35 hours of therapy. Some patients require (or request) a repeat or top-up procedure involving several additional sessions. These sessions are generally given to help sustain the long-term benefits of EECP. A search of the literature was undertaken to identify studies that could potentially inform the rate of repeat or top-up procedures. The search identified one study, based on the experience of patients in the IEPR, which examined the frequency and efficacy of repeat EECP for stable angina. Within 2 years of the initial course of EECP, the rate of repeat EECP was 18% (194/1078 patients), which occurred at a mean interval of 378 days after initial EECP. Assuming a fixed rate
### TABLE 7 Resource use and unit cost inputs used in the model

<table>
<thead>
<tr>
<th>Resource</th>
<th>Per annum cost</th>
<th>Per patient cost (n = 12)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital cost of machine (lifetime = 10 years)</td>
<td>£10,822</td>
<td>£902</td>
<td>Ken Miles, personal communication</td>
</tr>
<tr>
<td><strong>Equipment replacement costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One set of cuffs per year</td>
<td>£139</td>
<td>£12</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td>One set of hoses per year</td>
<td>£76</td>
<td>£6</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td>Pleth every 2 years</td>
<td>£53</td>
<td>£4</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td><strong>Consumables (for all 35 sessions)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound scan</td>
<td>–</td>
<td>£75</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td>Trousers</td>
<td>–</td>
<td>£16</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td>Gel</td>
<td>–</td>
<td>£8</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td>ECG electrodes</td>
<td>–</td>
<td>£110</td>
<td>Vasogenics price list (effective from April 2007)</td>
</tr>
<tr>
<td><strong>Staffing costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse (0.5 FTE)</td>
<td>£19,308</td>
<td>£1609</td>
<td>Wayne Sheedy, personal communication</td>
</tr>
<tr>
<td>M006 Medic (0.2 FTE)</td>
<td>£9808</td>
<td>£817</td>
<td>Wayne Sheedy, personal communication</td>
</tr>
<tr>
<td>Receptionist (0.25 FTE)</td>
<td>£4738</td>
<td>£395</td>
<td>Wayne Sheedy, personal communication</td>
</tr>
<tr>
<td>Overhead costs</td>
<td>–</td>
<td>£393</td>
<td>Wayne Sheedy, personal communication</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td></td>
<td>£4347</td>
<td></td>
</tr>
</tbody>
</table>

FTE, full-time employment.

with respect to time, the 2-year probability was converted to a 2-year rate and used to generate an annual probability. This annual probability of repeats decreased exponentially over time. To incorporate uncertainty in the estimates of repeat procedures, a beta distribution was used.

### Base-case analysis

The model results are presented according to a particular set of assumptions employed as part of the base-case analysis. The impact of employing alternative assumptions to those proposed in the base-case analysis is then explored using sensitivity analysis. The base-case assumes an average starting age, in the model, of 64 years and that 92% of subjects are male, based on the patient characteristics of the MUST-EECP trial.

Within the base-case approach, separate analyses have been undertaken assuming that QoL benefits from EECP are sustained for different durations. A worst-case scenario is considered in which the QoL gains from EECP are only maintained in the first year after treatment, and then lost in subsequent years. At the other extreme, a best-case scenario is considered in which the QoL benefits are assumed to last over a patient’s lifetime. Both the lifetime and the 1-year analyses model cost-effectiveness at the extremes. A more realistic approach is to consider the cost-effectiveness in terms of the proportion of patients likely to sustain benefits over time. Due to a lack of long-term evidence for QoL benefits following EECP, expert elicitation was used to arrive at a consensus on the likelihood of sustaining benefits long-term. The cost-effectiveness of EECP based on this consensus forms the base-case analysis.

### Sensitivity analysis

A number of alternative scenarios are considered as part of the sensitivity analysis. For each element, the position in the base-case analysis is outlined,
alongside the alternative assumptions applied. The sensitivity analyses are undertaken to assess the robustness of the base-case model results to variations in alternative assumptions related to key parameters in the model. Table 8 reports the alternative scenarios considered as part of the sensitivity analysis.

Cost-effectiveness results

The results of the model are presented in two ways. First, the mean lifetime costs and QALYs of the two strategies are presented and their cost-effectiveness compared, estimating ICERs where appropriate. The ICER compares the additional costs that one strategy incurs over another with the additional benefits, and represents the additional cost required to achieve one additional unit of outcome, QALY. To provide a reference point, the National Institute for Health and Clinical Excellence (NICE) uses a threshold cost per QALY of around £20,000–£30,000 to determine whether an intervention represents good value for money in the NHS. Consequently, if the ICER for EECP is less than £20,000 then EECP should be considered to be potentially cost-effective. ICERs within the range itself (i.e. between £20,000 and £30,000) are considered borderline, and an ICER above £30,000 is not typically considered to be cost-effective.

Second, the results of the probabilistic analysis using Monte Carlo simulation are used to calculate the combined impact of the model’s various uncertainties on the overall uncertainty surrounding the cost-effectiveness results themselves. To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used. The CEAC shows the probability that EECP is cost-effective, using alternative values for the threshold cost per QALY.

Results of the base-case analysis

The results of the base-case analysis, together with the best- and worst-case scenario for the duration of QoL benefits is reported in Table 9. The base-case results show that the ICER of EECP for angina (£18,643) is just below the lower bound of conventional thresholds used to identify whether a particular treatment is considered to be cost-effective in the NHS. At a threshold of £20,000 per QALY, the probability that EECP is more cost-effective than no treatment is 0.444. As the threshold cost per QALY increases, the probability that EECP is cost-effective increases. The relationship between the threshold ICER and the probability that EECP is cost-effective is shown clearly in the CEAC in Figure 5. The figure demonstrates how the probability increases as the threshold ICER increases (reaching close to 1 at a threshold of around £80,000).

The results of the worst-case scenario, in which QoL benefits from EECP are only sustained in

---

**TABLE 8** Details of the key elements of the base-case analysis, and how these vary in the sensitivity analysis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Element</th>
<th>Position in base-case analysis</th>
<th>Variation in sensitivity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Elicited expert values for the probability of sustaining QoL benefits from EECP over time</td>
<td>Linearly pooled values across experts with beta distribution fitted</td>
<td>Empirical values from each expert used in separate analyses</td>
</tr>
<tr>
<td>2</td>
<td>Costs of EECP</td>
<td>Total cost is £4347 per patient</td>
<td>Lower and higher costs assumed (from £1000 lower to £1000 higher)</td>
</tr>
<tr>
<td>3</td>
<td>Probability of repeat EECP sessions</td>
<td>Within 2 years of EECP, the rate of repeat procedures is 18%</td>
<td>Within 2 years of EECP, the rate of repeat procedures varied from 10% to 30%</td>
</tr>
<tr>
<td>4</td>
<td>Population</td>
<td>92% male, 8% female, Average age is 64 years</td>
<td>Separate analysis for men and women, Alternative starting ages assumed from 55 to 70 years</td>
</tr>
<tr>
<td>5</td>
<td>Discount rate</td>
<td>3.5% applied to both costs and outcomes</td>
<td>6% costs, 1.5% outcomes</td>
</tr>
</tbody>
</table>
**TABLE 9** Base-case estimates of mean lifetime costs and QALYs, together with best- and worst-case scenarios for the duration of QoL benefits

<table>
<thead>
<tr>
<th>Treatment analysis using pooled expert elicitation values</th>
<th>Probability of being cost-effective for the cost-effectiveness threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base-case analysis</strong></td>
<td>£20,000</td>
</tr>
<tr>
<td>EECP</td>
<td>£4750</td>
</tr>
<tr>
<td>No treatment</td>
<td>£0</td>
</tr>
<tr>
<td><strong>Worst-case scenario</strong></td>
<td></td>
</tr>
<tr>
<td>EECP</td>
<td>£4464</td>
</tr>
<tr>
<td>No treatment</td>
<td>£0</td>
</tr>
<tr>
<td><strong>Best-case scenario</strong></td>
<td></td>
</tr>
<tr>
<td>EECP</td>
<td>£5117</td>
</tr>
<tr>
<td>No treatment</td>
<td>£0</td>
</tr>
</tbody>
</table>

The first year after treatment, show that the ICER of EECP (£63,072) is well above the conventional thresholds of cost-effectiveness. Therefore, it is highly unlikely that EECP could be considered cost-effective if the duration of benefits from treatment is assumed to last only 1 year. The results of the best-case scenario, in which QoL benefits from EECP are fully sustained over a lifetime, show that the ICER of EECP (£5831) is well below conventional cost-effectiveness thresholds. The probability that EECP is cost-effective with sustained lifetime QoL gains approaches 1 at a much lower value of the ICER than the base-case analysis.

The cost-effectiveness results for EECP appear highly sensitive to the duration assigned to the QoL benefits that are assumed to be achieved with EECP. While the best-case scenario suggests that EECP is likely to be considered highly cost-effective based on conventional thresholds used to establish value for money by the NHS, the results from the base-case analysis are less clear cut. While the ICER presented for the base-case analysis still falls below the range of acceptable thresholds, it should be recognised that other factors (aside from the ICER itself) may be considered important. These factors may include the strength of evidence, the size of the affected population and whether a suitable comparator exists.49

![FIGURE 5 Cost-effectiveness acceptability curve for base-case analysis.](image-url)
Results of the sensitivity analysis

Table 10 details the results of each of the alternative scenarios considered within the sensitivity analysis. The table reports the ICER and the probability that EECP is cost-effective at thresholds of £20,000 and £30,000 per additional QALY. The base-case ICER of £18,643 provides the benchmark for assessing whether the cost-effectiveness results appear robust to particular assumptions made in the base-case analysis.

In the base-case analysis, the elicited expert values for the probability of sustaining QoL benefits from EECP over time were linearly pooled and a beta distribution fitted to the data. In a sensitivity analysis, the empirical values from each expert were considered separately to assess the cost-effectiveness. The ICERs from the five experts ranged from £10,664 to £28,158, indicating that the results are sensitive to the beliefs of the experts. The ICERs for experts 2 and 5 are well under threshold values conventionally considered to be cost-effective. The ICERs for experts 1 and 4 are similar but close to the upper threshold of £30,000 for cost-effectiveness. The ICER for expert 3 is closer to the pooled base-case ICER result. Because the results appear sensitive to the beliefs of the experts, the cost-effectiveness of EECP is highly sensitive to the probability of sustaining QoL benefits over time. A sensitivity analysis was also undertaken to assess the sensitivity of the beta distributional fit to the linearly pooled data by sampling from the empirical distribution of values. The results appear robust to the distributional form imposed on the data.

In the base-case analysis, the cost of EECP was £4347 per treatment. In a sensitivity analysis, a series of scenarios were considered by increasing/decreasing the costs of EECP to reflect the possibility of increased/decreased utilisation (patient throughput) in some centres. Clearly, if the costs are lower than those applied in the base-case analysis, the results will appear conservative to EECP. Reducing the costs by £1000 improved the cost-effectiveness, such that the ICER decreased to £14,354. Increasing the costs by £500 increased the ICER by £2145 per QALY. Increasing the costs by a further £500 increased the ICER by a similar amount again. If the costs are expected to be £3000 more than the base-case estimate of £4347 then it is unlikely that EECP can be considered to be cost-effective (with an ICER above the upper limit of £30,000 per QALY).

The base-case analysis assumed that the probability of repeat or top-up EECP sessions was 18% within 2 years of initial treatment. In a sensitivity analysis, this probability was varied from 10% to 30%. The corresponding results for the ICER varied from £18,021 to £19,413 respectively, indicating that the cost-effectiveness of EECP is quite robust to the likelihood of requiring additional treatment sessions.

The results of the base-case analysis were based on the average patient characteristics of entrants in the MUST-EECP trial (average age 64 years, 92% of sample subjects male). The cost-effectiveness results may also vary according to different patient characteristics (for example, men versus women, alternative ages). Heterogeneity in patient characteristics was explored using a series of separate scenarios. These scenarios were explored by varying the general population mortality rate according to the particular age and sex characteristics considered. Using this approach, the cost-effectiveness estimates in these scenarios are affected by the number of patients who can potentially stand to gain from sustained QoL improvements associated with EECP over time. The results demonstrate that cost-effectiveness is marginally improved in subgroups with the highest life expectancy (for example, women, age 55 years). However, differences between the subgroups are relatively minor, and the ICER for EECP remains around £18,000 per QALY across the subgroups.

Applying an alternative discount rate of 6% for costs and 1.5% for health outcomes (compared with 3.5% for both in the base-case analysis) improved the cost-effectiveness by a minor amount. The ICER remains below the lower bound of the £20,000 threshold.

Summary of cost-effectiveness results

The results of the base-case analysis demonstrate that the long-term maintenance of the QoL benefits of EECP appear central to the estimate of cost-effectiveness. If the QoL gains are maintained over the remaining lifetime of the patient then the cost-effectiveness of EECP appears clear, with the resulting ICER falling well below conventional thresholds of cost-effectiveness. Similarly, if the QoL gains are only maintained in the first year after treatment then the cost-effectiveness of EECP is also clear, but with a resulting ICER being well above the upper £30,000 threshold.
**TABLE 10** Summary of sensitivity analysis results

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Element</th>
<th>Variation in sensitivity analysis</th>
<th>ICER</th>
<th>Probability EECP is cost-effective for the cost-effectiveness threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£20,000</td>
</tr>
<tr>
<td>Base-case</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>£18,643</td>
<td>0.444</td>
</tr>
<tr>
<td>1</td>
<td>Elicited expert values for the probability of sustaining QoL benefits from EECP over time</td>
<td>Expert 1 empirical values</td>
<td>£28,158</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expert 2 empirical values</td>
<td>£12,235</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expert 3 empirical values</td>
<td>£21,473</td>
<td>0.386</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expert 4 empirical values</td>
<td>£27,245</td>
<td>0.213</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expert 5 empirical values</td>
<td>£10,664</td>
<td>0.805</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pooled expert empirical values</td>
<td>£18,237</td>
<td>0.463</td>
</tr>
<tr>
<td>2</td>
<td>Costs of EECP sessions</td>
<td>Lower and higher costs assumed (from £1000 lower to £1000 higher)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>–£1000</td>
<td>£14,354</td>
<td>0.618</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–£500</td>
<td>£16,499</td>
<td>0.529</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+£500</td>
<td>£20,788</td>
<td>0.372</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+£1000</td>
<td>£22,932</td>
<td>0.310</td>
</tr>
<tr>
<td>3</td>
<td>Probability of repeat EECP sessions</td>
<td>Within 2 years of EECP, probability varied from 10% to 30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10%</td>
<td>£18,021</td>
<td>0.469</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%</td>
<td>£18,424</td>
<td>0.452</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
<td>£19,117</td>
<td>0.428</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30%</td>
<td>£19,413</td>
<td>0.417</td>
</tr>
<tr>
<td>4</td>
<td>Population</td>
<td>Separate analysis for men and women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men (100%)</td>
<td>£18,666</td>
<td>0.444</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women (100%)</td>
<td>£17,996</td>
<td>0.464</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative starting ages assumed from 55 to 70 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55 years</td>
<td>£17,567</td>
<td>0.476</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 years</td>
<td>£17,951</td>
<td>0.466</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 years</td>
<td>£19,658</td>
<td>0.416</td>
</tr>
<tr>
<td>5</td>
<td>Discount rate</td>
<td>6% costs, 1.5% outcomes</td>
<td>£17,381</td>
<td>0.484</td>
</tr>
</tbody>
</table>

The more realistic question of how long the benefits are likely to be maintained in patients becomes a key consideration. The results from the base-case analysis, which are based on pooled expert beliefs about the durability of benefits, suggest that the overall cost-effectiveness is finely balanced, and difficult to determine without long-term RCT evidence on QoL gains from EECP. The sensitivity analysis examining separately the beliefs of each expert supports this conclusion.

**Value of information analysis: the decision to acquire more evidence**

In the previous sections, the expected cost-effectiveness of EECP in angina was assessed given the existing evidence available. The information on long-term effectiveness of EECP is scarce, and there is a prudent need to establish if EECP has a role for
treating angina and other forms of coronary artery disease. As such, an analysis of the EVI will help to prioritise the areas in which further research is needed in EECP. In the following sections, the potential value of future research is assessed, and a sufficient condition is presented for establishing if an additional clinical trial is required.

Methods for the expected value of information

The implications of the uncertainty associated with the cost-effectiveness of EECP are explored in this section by undertaking an analysis of the EVI. Analysis of the expected value of perfect information (EVPI) provides a formal quantitative approach to establishing if further primary research is indicated in light of the current decision uncertainty. It also provides an indication of where additional research is most valuable. The analysis produces an upper limit to the value of future research that could be undertaken, to reduce the uncertainty associated with a decision regarding the adoption of EECP routinely in the NHS.

Assuming that the objectives of the NHS are consistent with maximising health gains from available NHS resources, adoption decisions should be based on expected costs and benefits (i.e. on the ICER relative to some maximum willingness to pay for an additional unit of health gain) associated with the intervention. However, decisions based on expected values will be uncertain, and there will always be a chance that the wrong decision will be made, in which case there will be opportunity losses across the population of angina and other patients in terms of health benefit and resources forgone. Therefore, the expected cost of uncertainty can be determined jointly by the probability that a decision based on existing information will be wrong and the consequences of an incorrect decision. Uncertainty in the cost-effectiveness of EECP was represented using the cost-effectiveness acceptability curve (see Figure 5). This demonstrated that, at particular threshold values of the ICER, there exists significant uncertainty surrounding the cost-effectiveness of EECP, which has important implications for the value of conducting further research to support the adoption decision.

The expected cost of uncertainty associated with a decision based on current information is equivalent to the EVPI since perfect information would eliminate the possibility of making an incorrect decision. Furthermore, the EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future. EVPI is used to provide an upper bound on the value of additional research to that provided by the model. If the EVPI value is greater than the costs of additional research, consideration should be given to conducting further research to inform the adoption decision. In addition to providing a global estimate of the total cost of uncertainty related to all inputs in the model, EVPI can also be estimated for individual parameters (and groups of parameters) within the model. This partial EVPI analysis (termed EVPPI) can be used to identify the model parameters where more precise estimates would be most valuable.

The use of Monte Carlo simulation allows the expected costs of uncertainty associated with the initial adoption decision to be expressed as the proportion of iterations (or simulations) in which the uncertainty within the model results in an adoption decision other than that arising from maximising expected cost-effectiveness (i.e. expected net benefits). The benefits forgone are the difference in costs and outcomes (net benefit) between the optimal strategy for a given iteration and those of the strategy identified as optimal in the adoption decision (i.e. based on the expected cost-effectiveness estimates). The expectation of benefits forgone over all iterations represents the EVPI for an individual patient. More formally, this implies that, for a decision involving \( j \) treatments where net benefit (NB) is dependent upon a set of unknown parameters \( \theta \), the EVPI is the difference between the expected value of the decision made on the basis of existing information \( \text{max}_\theta \{E_\theta(\text{NB}(j, \theta))\} \), and the value of the decision made with perfect information \( \text{max}_\theta \{\text{NB}(j, \theta)\} \), averaged over all possible realisations of uncertainty \( E_\theta[\text{max}_\theta \{\text{NB}(j, \theta)\}] \):

\[
\text{EVPI} = E_\theta[\text{max}_\theta \{\text{NB}(j, \theta)\}] – \text{max}_\theta \{E_\theta(\text{NB}(j, \theta))\}
\]

The overall value of information for a population of patients who could benefit from EECP is determined by applying the EVPI per individual to the number of patients who would be affected by the information (i.e. the incidence) over the anticipated lifetime of the EECP technology:

\[
\text{EVPI} = P_0 \left[ I + \sum_{i=1}^{T} \frac{I_i}{1+i} \right]
\]

where \( P_0 \) is the prevalent population, \( I \) is the incidence in period \( t \), \( T \) is the total number of
periods for which information from research would be useful, and \( r \) is the discount rate.

The effective population who could potentially benefit from EECP is estimated to be around 7–10% of the number of patients who are affected by angina in the UK (Michael Chester, Liverpool Hope University, personal communication, 2008). The British Heart Foundation estimates that the prevalence of angina in the UK is 706,000 men aged between 55 and 75 years, and 392,000 women. This gives a total of just under 1.1 million. The incidence of angina is estimated to be around 52,000 new cases per year in all men in the UK and around 43,000 in women. Based on the base-case analysis where 92% of subjects are male, this implies a prevalence of about 680,880 and an annual incidence of around 51,280 for angina. Assuming that 10% of these patients could potentially benefit from EECP, this gives a prevalence of 68,088 and an annual incidence of 5128. The population EVPI is estimated using these values, and assumes that the information would be valuable for the 10-year lifetime of the EECP technology. A 3.5% annual discount rate is applied.

Individual patient and population EVPIs are calculated for the base-case model.

Results

Total expected value of perfect information

Figure 6 shows the population EVPI for the base-case model. The EVPI estimates are closely related to the threshold cost-effectiveness ratio and the associated probability that EECP is cost-effective. When the threshold for cost-effectiveness is low (for example, less than £5000 per QALY), EECP is not considered to be cost-effective under any scenario, and the associated probability that EECP is cost-effective is also low. In this case, there is minimal decision uncertainty that EECP is not optimal, therefore, additional information is unlikely to change this decision and so the estimates of EVPI are low. Similarly, when the threshold is considerably higher (for example, more than £50,000 per QALY), EECP is expected to be cost-effective under the base-case assumptions; therefore, the decision is less likely to be changed by further research. Hence, the EVPI falls to zero after £50,000 per QALY. The EVPI reaches a maximum at the point where the threshold for cost-effectiveness is equal to the expected ICER of EECP. This maximum occurs when the decision is most uncertain on whether to adopt or reject EECP based on current evidence (i.e. at £18,643 per QALY). Given that the EVPI places an upper bound on the value of conducting further research, the EVPI can be interpreted as follows.

If the population EVPI exceeds the expected costs of additional research then it is potentially cost-effective to conduct further research. For example, if additional research in EECP is expected to cost £20 million then additional research is potentially cost-effective if the threshold is between £11,000 and £43,000 per QALY.

The population EVPI can be scaled back to provide results for the individual per patient EVPI. This allows decision-makers to apply the results to the potential size of their own population of interest. Table 11 provides a summary of the population and
TABLE 11  Individual patient and population EVPI for selected values of the threshold for the base-case model

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Individual patient EVPI for the cost-effectiveness threshold</th>
<th>Population EVPI for the cost-effectiveness threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£20,000</td>
<td>£30,000</td>
</tr>
<tr>
<td>Base-case</td>
<td>£971.29</td>
<td>£440.16</td>
</tr>
</tbody>
</table>

individual EVPI estimates for selected threshold values.

**Partial expected value of perfect information**

The total EVPI provides a useful estimate of the uncertainty surrounding the adoption decision as a whole, but it does not provide an indication of where further research would be considered most valuable. The value of reducing the uncertainty surrounding particular input parameters in the model can be established by estimating the expected value of partial perfect information (EVPPI). This considers particular elements of the decision problem in order to direct and focus research towards the specific areas in which the elimination of uncertainty has the most value. This can be particularly relevant to the design of any future research (see Expected value of sample information). The analysis of EVPPI can be conducted in a similar way to the EVPI for the decision as a whole but it requires substantial additional computations. Formally, the EVPPI for a parameter (or subset of parameters) \(\phi\), is the difference between the expected value of the decision made on the basis of existing information (\(\max_j[\mathbb{E}_{\theta}(\mathbb{E}_{\phi}(\text{NB}(j, \theta)))]\)) (as with the calculation of decision EVPI) and the value of the decision made with perfect information about \(\phi\) (\(\max_j[\mathbb{E}_{\phi}(\text{NB}(j, \theta))]\)). Where perfect information about the parameter \(\phi\) has no impact on the decision, the information has no value. The value of the decision made with perfect information about \(\phi\) is averaged over all possible realisations of uncertainty (\(\mathbb{E}_{\theta}[\max_j(\mathbb{E}_{\phi}(\text{NB}(j, \theta)))]\)) to reflect the fact that the parameter can resolve at any point within the distributions:

\[
\text{EVPPI}_{\phi} = \mathbb{E}_{\phi}[\max_j(\mathbb{E}_{\phi}(\text{NB}(j, \theta)))] - \max_j[\mathbb{E}_{\phi}(\text{NB}(j, \theta))]
\]

There are three groups of uncertain parameters in the base-case model. These relate to:

1. the 1-year QoL improvement from EECP in the MUST-EECP trial
2. the probability of sustaining QoL benefits in each subsequent year
3. the probability of repeat top-up procedures.

The EVPPI for each of these parameters [or groups of parameters in the case of (2) above] is calculated over a range of threshold values.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Parameters</th>
<th>Individual patient EVPPI for the cost-effectiveness threshold</th>
<th>Population EVPPI for the cost-effectiveness threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case</td>
<td>All parameters</td>
<td>£971.29</td>
<td>£440.16</td>
</tr>
<tr>
<td>1</td>
<td>1-year QoL improvement</td>
<td>£784.68</td>
<td>£340.35</td>
</tr>
<tr>
<td>2</td>
<td>Probability of sustaining QoL benefits in subsequent years</td>
<td>£379.80</td>
<td>£10.14</td>
</tr>
<tr>
<td>3</td>
<td>Repeat top-up procedures</td>
<td>£0.00</td>
<td>£0.00</td>
</tr>
</tbody>
</table>
The probability of sustaining these QoL gains in each subsequent year appears to have a more moderate influence on the overall decision uncertainty (based on the base-case assumptions). The estimates of EVPPI for these parameters are shown in Figure 7, based on a wider range of threshold values. The probability of repeat top-up procedures demonstrates little value to additional research.

Expected value of sample information

In the previous sections, the EVPI and EVPPI set an upper limit on the returns to further research, i.e. if the population EVPI is greater than the expected costs of further research, then further studies should be considered. However, to fully inform the research decision, the most efficient research design needs to be established; for example, the type of study to be conducted, the optimal sample size, the optimal allocation of patients within a clinical trial, the appropriate follow-up time and which end points should be included. To establish the most appropriate design, the marginal benefits and marginal costs of gathering sample information need to be considered. The same framework of EVI analysis can be extended to establish the EVSI for a particular research design. The difference between the EVSI and the costs of sampling is the ENBS. The ENBS provides a measure of the payoff to the health system from research, and can be calculated for a range of sample sizes and alternative designs of research. Therefore, it provides a sufficient condition for deciding to conduct more research, i.e. if the ENBS is greater than zero then the marginal benefits of gathering the sample information exceed the marginal costs. The optimal design (e.g. sample size, follow-up duration, etc.) is characterised by that which maximises the ENBS.25

The issue of which information to obtain first requires calculation of the EVSI. This places an upper limit on the cost of conducting a new trial for a given sample size \( n \). In other words, it is the maximum value of conducting a new trial and it depends on the number of patients projected to enrol in the new study. If the cost of the new study is less than the EVSI, the new trial is considered to be worthwhile. The EVSI approach considers the payoff (expected net benefit) that could be obtained if decisions were based on having additional sample information. This is done by predicting possible sample results that might be expected from a particular study with sample size \( n \). The sample information allows an update of imperfect prior information about model parameters, by combining the prior knowledge with each of the possible sample results to form a number of possible predicted posterior results.25

The expected net benefit for the decision problem is calculated for each of these possible posteriors. The difference between the expected net benefit of the decision based on the predicted posteriors and the expected net benefit based on prior current information gives the EVSI for a sample of size \( n \). More formally, a sample \( n \) on a set of unknown parameters \( \theta \) will provide a sample result \( D \). If \( D \) was known in advance, the expected
value of the decision would be found by averaging over the posterior distribution of the NB of each treatment \( j \) given the new data \( D \) (\( \max_j [E_{\theta|D}(NB[j, \theta])] \)). However, as \( D \) is not known in advance, the expected value of the decision is taken by averaging over the predictive distribution of possible values of \( D \) conditional on \( \theta \) (\( E_{\theta}[\max_j [E_{\theta|D}(NB[j, \theta])] \)). The EVSI is then expressed as:

\[
EVSI(n) = E_{\theta}[\max_j [E_{\theta|D}(NB[j, \theta])] - \max_j [E_{\theta}(NB[j, \theta])]
\]

which measures the additional value of a decision based on sample \( n \) rather than on current information.

Analogous to population EVPI, the overall value of sample information for a population of patients who could potentially benefit from EECP is determined by applying the EVSI per individual to the number of patients who would be affected by the information when it becomes available over the lifetime of the technology:

\[
pEVSI(n) = EVSI(n)^* \left( \frac{P_0 + \sum_{i=1}^{T} I_i}{(1+r)^{FU}} \right) + \sum_{t=FU+1}^{T} \frac{I_t}{(1+r)^t}
\]

where \( P_0 \) is the prevalence at time \( T = 0 \), \( FU \) is the follow-up length of the trial, \( I_i \) is the incidence in period \( i \), \( I_t \) is the incidence in period \( t \), \( T \) is the total number of periods for which information from research would be useful, and \( r \) is the discount rate.

To obtain the societal payoff to the proposed research, the population EVSI needs to be compared with the costs of sampling. Assuming that the proposed clinical trial has two treatment arms with equal allocation of patients across the two treatments, the cost of sampling \( (C) \) for a 1-year follow-up is given by:

\[
C(n) = FC + RC * n + (P_0 + I_1, -n)^* \\
\{NB'(T = 1) - NB^{ST}(T = 1)\} + (n/2)^* \\
\{NB'(T = 1) - NB'(T = 1)\}
\]

where FC is the fixed cost of the proposed research, RC is the reporting costs, \( P_0 \) is the prevalence at time \( T = 0 \), \( I_1 \) is the incidence in year 1, NB' is the expected net benefit for the optimal treatment based on prior current information, NB^{ST} is the expected net benefit for standard therapy based on prior current information, and NB^* is the expected net benefit of the treatment which is not optimal, based on prior information. Accounting for the length of follow-up of the trial, the third term represents the expected opportunity cost of a trial, when a decision on whether to adopt a particular treatment or not is delayed while the trial is undertaken, i.e. standard therapy is retained during the trial follow-up period. Therefore, in the third term, the prevalence at time \( T = 0 \) (minus the number of patients who entered the trial, \( n \) and the incidence during the trial follow-up period will be allocated to standard therapy while the trial is undertaken. Consequently, if standard therapy is not cost-effective, there will be an expected opportunity cost equivalent to \( (NB'(T = 1) - NB^{ST}(T = 1)) \), whereas if standard therapy is cost-effective, there will be no loss. The fourth term accounts for the opportunity cost of allocating half the trial sample to the non-optimal treatment during the trial period.

The societal payoff to the proposed research, known as the ENBS, is the difference between the expected benefits of sampling \( (pEVSI) \) and the expected cost of sampling \( (C) \):

\[
ENBS(n) = pEVSI(n) - C(n)
\]

This provides a sufficient condition for deciding to conduct more research. If the \( ENBS(n) > 0 \) for any sample size, then further research is justified. The ENBS also provides a framework for the efficient design of the clinical trial. The optimal sample size \( n^* \) for the proposed trial is where the ENBS reaches a maximum. A number of alternative research designs across a range of dimensions can be investigated within the framework. However, it is worth noting that the computations for EVSI can be very challenging when dimensions are added to the design space.54

For EECP, a simple research design might consist of an RCT allocating equal numbers of entrants to EECP versus standard care. In this case, enumeration of a sufficient range of sample sizes will yield the optimal sample size \( n^* \) that maximises the ENBS. This optimal sample size indicates how many patients should be enrolled in the trial for it to provide the highest payoff. Given the lack of evidence regarding the long-term maintenance of QoL benefits from EECP, the length of follow-up of the trial may be a further design feature to be optimised along with \( n \).
Population EVSI and the ENBS are calculated for the base-case model. The optimal sample size and proposed length of follow-up are determined.

**Results**

**Population expected value of sample information for the decision problem**

Figure 8 shows the population EVSI for the base-case model for selected thresholds, assuming a linear relationship between inputs and expected costs and outcomes. The assumption of linearity has only a limited impact on the results (see Appendix 6). The EVSI corresponds to a 4-year clinical trial design that includes all the model parameters as end points, and in which the entrants are allocated equally between treatment arms. The EVSI is closely related to the threshold cost-effectiveness ratio in the same way as demonstrated with EVPI. For example, the EVSI is highest at the threshold of £20,000 at which the decision is more uncertain, reflecting the relationship between the population EVPI and the threshold seen in Figure 6. The EVSI increases as the sample size is increased, but at a declining rate. For this trial design, the EVSI will eventually approach the population EVPI for the particular threshold value as the sample size becomes very large.

The EVSI in Figure 8 provides the upper limit on the cost of conducting a new trial for a given sample size and cost-effectiveness threshold. It provides an estimate of the benefits of sample information, but these need to be compared with the costs of sampling.

**Expected net benefit of sampling for the decision problem**

By comparing the EVSI in Figure 8 with the costs of sampling, the optimal sample size for a clinical trial can be identified when the ENBS reaches a maximum. Figure 9 shows the ENBS for the decision problem at cost-effectiveness thresholds of £10,000 and £20,000 per QALY. At a threshold of £30,000, the ENBS is negative, indicating that the increased opportunity costs of sampling for a 4-year trial follow-up design outweigh the marginal gains generated from additional sample information. At the threshold of £30,000, the probability that EECP is cost-effective is higher. Consequently, there are higher opportunity costs of benefits forgone by allocating patients who could potentially benefit from EECP to standard therapy during the 4-year trial follow-up period when the decision-maker is willing to pay £30,000 per additional QALY.

In Figure 9, the fixed costs of sampling are excluded as they do not influence optimal sample size or allocation. The reporting costs for patients enrolled in the treatment arms were assumed to be £300 per patient per follow-up year. The marginal costs of sampling with equal allocation are constant. Therefore, because the marginal value of sample information increases at a diminishing rate as the sample size increases but the costs of sampling increases in proportion to the number of patients enrolled in the trial, the ENBS will reach a maximum before declining. In Figure 9, at a threshold of £20,000 per QALY, the ENBS reaches a maximum of £87.9 million at an optimal sample size of 900 patients. If the ENBS of £87.9 million is greater than the fixed costs of the research,
then the proposed 4-year clinical trial with equal allocation can be considered cost-effective.

Because the EVSI depends on the cost-effectiveness threshold, the ENBS also depends on the threshold, and so in Figure 9 there are different optimal sample sizes for different thresholds. For the threshold of £20,000, the ENBS curve is relatively flat at its maximum. Therefore, sample sizes slightly more or less than the optimal size of approximately 900 have little impact on the ENBS. The relationship between ENBS and sample size is dependent on the costs of sampling. If the costs of sampling are expected to be substantially more than those estimated in this example, the ENBS can be expected to fall from its maximum more quickly. At a threshold of £10,000 per QALY, the optimal sample size is much less (n* = 340) than at the threshold of £20,000. This is because further research is less valuable at this threshold. There is minimal decision uncertainty that EECP is not considered to be cost-effective at the threshold of £10,000 and, therefore, additional information is unlikely to change the adoption decision.

The ENBS and optimal sample size in Figure 9 is positive, indicating that this particular research design would be cost-effective and that further research is needed if the decision-maker is willing to pay less than £30,000 per additional QALY. The design employed in this example corresponds to a single trial with equal allocation between treatment arms. It also corresponds to a trial with a 4-year follow-up. The EVSI for the decision problem is based on a design that could potentially provide information on all the uncertain parameters in the model. As the elicitation exercise provided prior information on the sustained duration of QoL benefits up to year 4, the posterior predictions based on sample information were calculated up to year 4. Beyond that, the model assumes that the proportion of patients sustaining benefits in each subsequent year (conditional on sustaining benefits in the previous year) is equivalent to that in year 4. In the following section, the appropriate length of follow-up of the trial is considered as a further design feature.

### Appropriate length of follow-up of clinical trial

The appropriate length of follow-up of the clinical trial is an important design feature in the case of EECP since the evidence for the long-term maintenance of QoL benefits is limited. Figure 10 shows the ENBS for different lengths of follow-up at a threshold of £20,000 per QALY. In the 1-year follow-up, it is assumed that information is revealed on the QoL gains from EECP relative to standard care (i.e. no EECP treatment) and on the number of patients requiring additional repeat sessions. The ENBS reaches a maximum of £84.2 million at an optimal sample size of 1450. In the 2-year follow-up, it is assumed that the same information from the 1-year follow-up is revealed but, in addition, information is revealed on the sustained duration of QoL benefits in the second year after treatment. The ENBS in this case is very similar to that in the 1-year follow-up and reaches a maximum of £84.1 million at a lower optimal sample size of 1200. In the 3-year follow-up, the same information as the 2-year follow-up is revealed, but the sustained duration of QoL benefits would be considered.
benefits from year 2 to year 3 is also revealed. In this case, the ENBS falls below the ENBS for a 2-year follow-up because the increased opportunity costs incurred by withholding sample information for an additional year outweigh the marginal gains generated from the additional year’s information. The ENBS for a 3-year follow-up reaches a maximum at £81.7 million at an optimal sample size of 950. The ENBS for a 4-year follow-up is higher than the other periods of follow-up because the model assumes that the proportion of patients sustaining benefits in the fourth year is unlikely to differ substantially in subsequent years. In this case, information regarding the sustained benefits up to 4 years after treatment is more valuable than any shorter period of follow-up. Clearly, a trial involving a fifth year of follow-up would provide even further information (assuming that the additional costs incurred by following patients for another year do not outweigh the additional information gains), but at some point of follow-up assumptions need to be made regarding the sustained duration of benefits beyond the follow-up period. Based on the results of Figure 10, a 4-year follow-up with an optimal sample size of 900 patients allocated equally across treatment arms would provide the greatest returns to research.

Summary of value of information results

The cost-effectiveness results for EECP appear highly sensitive to the duration of sustained QoL benefits that are assumed to be achieved with treatment. The uncertainty surrounding the duration and also the actual estimate of the QoL gains from treatment results in a significant cost of uncertainty reflected in high EVPI estimates at particular cost-effectiveness thresholds. The population EVPI estimates suggest that further research in this area is likely to be of significant value. The EVPI for individual parameters highlighted that potential future research would be of most value directed towards obtaining more precise estimates of the QoL following EECP treatment and the duration that these QoL benefits are expected to be maintained.

Given that there is potential value to future research, a clinical trial design was proposed. This trial design considered an equal allocation of patients between the arms of the proposed trial. Although it depends on the cost-effectiveness threshold, the ENBS is positive for most sample sizes, indicating that further experimental research will be efficient. Given that the threshold for cost-effectiveness is £20,000 per QALY, the highest expected returns to additional research will come from a trial with a 4-year follow-up and an optimal sample size of 900 (i.e. 450 entrants to each arm of the proposed trial). Clearly, these conclusions are based on the set of assumptions employed in the base-case model. In particular, these recommendations are based on a population of patients with angina severity similar to MUST-EECP patients.
Chapter 4

Discussion

Statement of principal findings

Clinical evaluation

A systematic review was conducted to assess the clinical effectiveness and safety of EECP for treatment of stable angina and heart failure. There is a paucity of RCTs investigating the effectiveness of EECP in these groups of patients. Of the four controlled studies of EECP for the treatment of stable angina,17–20 only one was an RCT17 (the MUST-EECP trial), and a single RCT (the PEECH trial)21 represented the total body of controlled clinical studies in heart failure.

The evidence for the clinical effectiveness of EECP in chronic stable angina was extremely limited. The MUST-EECP trial provided the most reliable investigation of EECP in angina but, even so, the results have to be interpreted with caution owing to limitations in the quality of the study analysis and the short duration of follow-up. On the other hand, this study did use a sham EECP as placebo and may therefore have understated the effects of EECP in practice: the placebo effect of sham EECP may well be clinically significant and so any benefit of active EECP over that of sham EECP is likely to be smaller than the benefit seen with EECP compared with usual care. The MUST-EECP trial reported a mean 37-second improvement in time to exercise-induced ischaemia with EECP compared with a 4-second deterioration with sham EECP at the end of treatment; improvement in this outcome is a key objective of angina management according to European and US professional organisations. There were also limited improvements in mean exercise duration, number of angina episodes and NTG use, but these did not reach statistical significance (possibly because there were too few patients), and again the clinical significance is uncertain. Although there was evidence of a benefit with EECP on QoL 12 months after treatment, this was based on just under half of the original sample, so this finding should be treated with caution as this may not have been representative of the whole sample. With the exception of QoL, the outcomes were assessed only at the end of treatment, i.e. following 35 sessions, so the long-term effects of EECP in angina patients could not be determined.

Mortality or MACEs were not assessed in this trial; therefore there is no evidence available from RCTs on these important clinical outcomes. There is evidence, based on a comparison of two registries, that 1-year all-cause mortality is similar in patients that have received EECP and PCI (1.3% and 3.2% respectively). In addition to some weaknesses in the internal validity of the trial, there are also limitations on the generalisability of the results of the trial. In common with the two large angioplasty studies (RITA-227 and COURAGE55), the substantial exclusion criteria and the large proportion of participants with Class I or II symptoms limit the extent to which the findings can be generalised to all patients with refractory stable angina.

Furthermore, although many (if not all) of the patients in the MUST-EECP trial were experiencing angina while receiving medical therapy, refractory stable angina has a variety of definitions, some of which require the patient to have angina more severe than that seen in the MUST-EECP trial, i.e. refractory to both medication and surgery.56,57

The PEECH trial evaluated the effects of EECP in patients with mild to moderate heart failure. As with the stable angina trial, the focus was on improvement in symptoms and exercise duration: cardiac-related mortality was not reported. In this trial, there was an improvement with EECP compared with usual care control on all outcome measures at the end of treatment. At 6 months’ follow-up, the benefit of EECP in terms of improved exercise duration and improved NYHA class had been maintained, but not in terms of peak VO₂ or QoL. The clinical benefit to heart failure patients of a 35-second increase in mean exercise duration and a difference of 10% achieving a minimum 60-second increase in exercise duration is unclear. The inclusion/exclusion criteria were extensive; therefore, the trial population may not accurately reflect patients who would typically be seen in clinical practice for this therapy. The limited follow-up means that the effects of EECP on the long-term outcomes of these patients cannot be ascertained.

Adverse events associated with EECP were common in the RCTs, with around 12% of patients withdrawing due to AEs. The most commonly
Discussion

reported device-related AEs were leg or back pain, or skin abrasion, bruise or blister. Non-device-related AEs were also common, and in these studies it was not established whether the adverse effects classified as ‘non-device related’ could be due to the wider impact of EECP on the cardiovascular system. Thus, the adverse effects of EECP may be a clinically relevant limitation to the effectiveness of EECP.

Economic evaluation

The decision problem addressed by the decision analytic model relates to the cost-effectiveness of EECP in adults with chronic stable angina. The model evaluates a strategy of EECP treatment compared with no treatment, and is structured to project HRQoL benefits beyond the 1-year trial follow-up period of MUST-EECP.17

The base-case analysis for a population of patients with angina severity similar to MUST-EECP demonstrates that the long-term maintenance of QoL benefits of EECP is central to the estimate of cost-effectiveness. If QoL benefits of EECP are assumed to be maintained for no more than 1 year after treatment, EECP does not appear to be cost-effective in the NHS, as defined by NICE’s cost-effectiveness threshold range.28 In contrast, if QoL benefits are maintained over a lifetime, the cost-effectiveness of EECP appears clear, with a resulting ICER well below conventional thresholds of cost-effectiveness. The base-case analysis, based on pooled expert beliefs about the durability of QoL benefits, suggests that the overall cost-effectiveness of EECP is finely balanced and difficult to determine without evidence from an RCT with long-term follow-up about QoL from EECP. The sensitivity analysis examining the beliefs of each clinical expert separately on durability of benefits leads to conflicting conclusions about the cost-effectiveness of EECP.

The cost-effectiveness model reveals uncertainties surrounding the duration of treatment benefits and also the actual estimate of the 1-year QoL improvement from EECP. The value of information analysis suggests that future research in this area is likely to be of significant value. This research should be directed towards obtaining more precise estimates of the QoL following EECP treatment and of the duration over which these benefits are expected to be maintained. The ENBS is positive for a range of cost-effectiveness thresholds and sample sizes, indicating that further experimental research in EECP would be efficient. For this particular patient population (MUST-EECP type patients), a clinical trial design with a 4-year follow-up and a sample size of 900 is suggested by the value of information analysis. This proposed trial is expected to give the highest expected returns to research, based on the set of assumptions employed in the base-case model.

Strengths and limitations

of the assessment

A rigorous review of the research literature on the effects of EECP for the treatment of refractory or chronic stable angina and heart failure has been conducted, capturing the most recent evidence relating to EECP. However, despite this, the assessment of the clinical evidence is clearly limited by the paucity of evidence. Only five studies identified in our searches were eligible for inclusion, and, of these, only two were RCTs (n = 326). The remaining three studies had significant methodological flaws, which seriously limit the value of their findings. One was a comparison of two registries in which the baseline characteristics of the two groups were substantially different. The other two studies had a very small number of participants, and assignment to treatment was self-selection. In addition, the evidence available from the RCTs was derived from mainly short-term outcomes. No RCT evidence or reliable data were available regarding mortality or MACEs.

Given that there is no existing cost-effectiveness evidence that provides a basis for informing policy decisions regarding the use of EECP in the NHS, a new decision-analytic model has been developed. While the cost-effectiveness model addresses this limitation by evaluating EECP treatment in stable angina, the model has several potential limitations that need to be considered in conjunction with the results. Clearly, the model output is dependent on the parameter inputs that are used. The QoL estimates applied in the model remain highly uncertain. Although there are several studies reporting on the QoL of patients following EECP treatment, most of these use a simple five-point rating scale that poses several problems if directly applied within a cost-effectiveness analysis. To date, there are no studies that directly quantify the long-term impact of EECP using a generic utility measure such as the EQ-5D.28

This represents a major limitation when trying to establish the cost-effectiveness of an intervention,
as the use of these measures provides a clearer basis for establishing value for money in the NHS when decisions need to be made across a range of healthcare interventions and programmes. Therefore, it is important to establish that the additional value provided by EECP to the NHS will offset any benefits lost through resource displacements (potentially in different patient populations). The absence of direct data using a generic utility instrument represents a major omission from the existing evidence base for EECP. In the absence of these data, alternative approaches were used. For the 1-year QoL estimate, a mapping algorithm was used to convert the aggregate SF-36 data from the MUST-EECP trial into a utility-based measure (EQ-5D). The process of mapping between the instruments, and the lack of individual patient level data introduce an additional source of uncertainty. However, in the absence of alternative data, the current estimates represent the best available QoL values. In the absence of any long-term estimates for QoL, expert elicitation techniques were employed to quantify the durability of benefits. A number of separate scenarios demonstrated that the results were sensitive to the beliefs of the clinical experts. Therefore, the model results clearly demonstrate that the cost-effectiveness of EECP is extremely sensitive to the duration over which the benefits are likely to be maintained.

The decision model does not consider the impact of EECP treatment on ‘hard’ outcomes such as death or major adverse clinical events. No comparative studies of EECP address outcomes of death or clinical events such as MI. Consequently, no reliable estimates could be used to populate a long-term prognostic model of EECP for angina. The cost-effectiveness estimates for EECP can be considered conservative if EECP does, in fact, lead to a reduction in the risk of major clinical events over and above the reduction from standard care.

There is uncertainty regarding the need for repeat EECP treatment sessions. These repeat or top-up sessions have implications for costs and QoL, but there is little focus on this issue in the published research literature. Although the value of information analysis reported here indicates that there is little uncertainty in the probability of repeat top-up procedures, it should be recognised that owing to structural uncertainties in the model this uncertainty may be underestimated. It should also be recognised that the treatment costs of EECP itself remain uncertain. The costs used in the model are based on a reasonable approximation of the resource costs associated with the treatment sessions. However, it should be noted that different centres in the UK are currently charging different prices to purchasers for EECP therapy. This may reflect the increased/decreased utilisation (patient throughput) in some centres. The cost of EECP may change if departments are run more effectively. The analysis does not take into account escalating medical costs that may occur over time. Costs of the non-EECP option in the cost-effectiveness analysis may be underestimated, given that there could be baseline medical costs associated with hospitalisations.

The decision model only considers the cost-effectiveness of EECP in patients with chronic stable angina, similar in severity to MUST-EECP patients. Our clinical advice is that, currently, EECP is more widely used in angina than in heart failure. Owing to the limitations of existing evidence in relation to patients with heart failure, separate cost-effectiveness analyses were not undertaken for the two forms of heart disease. Consequently, the generalisability of these findings to a broader range of patients who could potentially benefit from EECP should be viewed with due caution. The modelling framework developed here for angina can be readily employed in other populations, including patients with heart failure, as and when further evidence emerges.

The available trials and case series are predominantly US based. There are very few UK-based data represented in the research literature. Therefore, it is uncertain how generalisable to the UK context the findings of the clinical evaluation are.
Chapter 5

Conclusions

The results from a single RCT do not provide firm evidence of the clinical effectiveness of EECP in chronic or refractory stable angina. Furthermore, better quality RCTs are required to investigate the benefit of EECP in terms of time to ST segment depression, exercise duration, angina frequency and patients’ requirement for NTG, and if these outweigh the common adverse effects associated with this intervention.

Similarly, the results from a single RCT in heart failure do not provide firm evidence of the clinical effectiveness of EECP. Statistically significant modest benefits were seen in terms of exercise duration and NYHA classification; however, their clinical significance is unclear. These effects need to be investigated in further RCTs.

To date, the impact of EECP on mortality or major adverse cardiovascular events has not been investigated in angina or heart failure.

The long-term maintenance of QoL benefits of EECP is central to the estimate of cost-effectiveness. If QoL benefits of EECP are assumed to be maintained for no more than 1 year after treatment, EECP does not appear to be cost-effective in patients with angina severity similar to those in the MUST-EECP trial. Assuming that QoL benefits are maintained over the remaining lifetime of the patient, the cost-effectiveness of EECP appears clear, with a resulting ICER well below conventional thresholds of cost-effectiveness. Based on current evidence, EECP appears cost-effective for this patient population, but there is significant value to future research informing the long-term maintenance of QoL benefits from EECP.

Recommendations for research

The limited evidence suggesting that EECP may be an effective treatment for chronic or refractory stable angina and mild to moderate heart failure would indicate that further RCTs are warranted. The available data from case series and the RCTs indicate that troublesome adverse effects may limit the benefits achievable with EECP. The investigation of adverse effects should be an important outcome in any future RCT. The value of information analysis undertaken in this report suggests that further research in this area is likely to be of significant value. Long-term follow-up trials assessing QoL from EECP in both chronic stable angina and heart failure are required. There is also an important need to establish the efficacy of EECP in patients with truly refractory severe angina, which is much more severe than that found in MUST-EECP patients.

Additional research is also required to address the following uncertainties detailed in our report:

- generalisability of findings to UK practice
- impact of EECP on mortality
- impact of EECP on major adverse cardiovascular events
- difference between QoL associated with EECP and other comparative treatments
- duration of beneficial effects
- efficacy in different subgroup populations; in particular, symptomatic relief in patients with truly refractory severe angina
- effectiveness of different EECP treatment regimens.
We would like to thank those authors who responded to our requests for further information. In particular, we would like to thank the clinical experts who participated in the elicitation exercise. Claire McKenna would also like to thank Laura Bojke and Stefano Conti for their advice on specific aspects of the economic modelling.

Contribution of authors

Michael Chester and John Cleland provided technical and clinical advice and commented on drafts of the report. Karl Claxton, Neil Hawkins and Claire McKenna were involved in the cost-effectiveness section, study selection, development of the economic model and report writing, as was Mark Sculpher, who also took overall responsibility for the economic component. Kate Light devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Catriona McDaid and Sara Suekarran were involved in the clinical effectiveness section, including writing the protocol, study selection, data extraction, quality assessment, data analysis and report writing. Nerys Woolacott provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the review.
References


35. Ara R, Brazier J. Deriving an algorithm to convert the 8 mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health* 2008;11(7):1131–43. Published online 2008.


44. Government Actuary’s Department. *Interim life tables*. Office for National Statistics; 2007. URL:


References


References


120. Soran O, Kennard ED, Bart BA, Kelsey SE. Impact of external counterpulsation treatment on emergency department visits and hospitalizations in refractory angina patients with left ventricular dysfunction. Congest Heart Fail 2007;13:36–40.


125. Sun J. Hemodynamic study of external counterpulsation with left and right cardiac catheters in 15 cases. Chung Hua I Hsueh Tsa Chih 1991;19:375–8, 98.


Main searches

**MEDLINE (Ovid Online – www.ovid.com/)**
1950–October 2007 (week 4)
Search on 1 November 2007
Retrieved 206 hits

**MEDLINE In-process (Ovid Online – www.ovid.com/)**
October 31 2007
Search on 1 November 2007
Retrieved 13 hits

**EMBASE (Ovid Online – www.ovid.com/**
1980–2007 (week 43)
Search on 1 November 2007
Retrieved 190 hits

**CINAHL – Cumulative Index to Nursing & Allied Health Literature (Ovid Online – www.ovid.com/**
1982–October 2007 (week 4)
Search on 1 November 2007
Retrieved 36 hits

Search strategy

1. external counterpulsation.ti,ab.
2. external counter pulsation.ti,ab.
3. eecp.ti,ab.
4. peech.ti,ab.
5. must eecp.ti,ab.
6. or/1–5
7. 6
8. limit 7 to yr="1980 – 2007"

**Cochrane Database of Systematic Reviews (The Cochrane Library – www.thecochranelibrary.com/**
Issue 4 2007
Search on 1 November 2007
Retrieved 1 hit

**CENTRAL (The Cochrane Library – www.thecochranelibrary.com/**
Issue 4 2007
Search on 1 November 2007
Retrieved 15 hits

Search strategy

#1 “external counterpulsation”
#2 “external counter pulsation”

#3 (eecp)
#4 “must eecp”
#5 (peech)
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 (#6), from 1980 to 2007

**DARE – Database of Abstracts of Reviews of Effects, HTA [Health Technology Assessment Database and NHS EED (NHS Economic Evaluation Database)]**

Search on 5 November 2007
Retrieved 1 hit from DARE, 8 hits from HTA and 0 hits from NHS EED

Search strategy

1. s external(w)counterpulsation
2. s external(w)counter(w)pulsation
3. s eecp
4. s peech
5. s must(w)eecp
6. s s1 or s2 or s3 or s4 or s5
7. s @1980:2007
8. s s6 and s7

**Inside Conferences (Dialog File 65 on DialogClassic Web – www.dialogclassic.com/**
Search on 6 November 2007
Retrieved 0 hits

Search strategy

1. External (w) counterpulsion/ti,ab,de
2. External (w) counter (w) pulsation/ti,ab,de
3. Eecp/ti,ab,de
4. Must (w) eecp/ti,ab,de
5. peech/ti,ab,de
6. s1:s5
7. py=2005:2007
8. s6 AND s7

**NRR – National Research Register (www.nrr.nhs.uk/**
2007; Issue 4
Search on 9 November 2007
Retrieved 8 hits

Search strategy

1. external counterpulsation
2. external counter pulsation
Update searches

The strategies for the main searches were re-run and the results reduplicated against the original results.

- MEDLINE (Ovid Online – www.ovid.com/) – March week 2 2008 – 4 new records
- MEDLINE In-process (Ovid Online – www.ovid.com/) – March 25th 2008 – 1 new record
- CINAHL – Cumulative Index to Nursing & Allied Health Literature (Ovid Online – www.ovid.com/) – March week 3 2008 – 3 new records
- Cochrane Database of Systematic Reviews (The Cochrane Library – www.thecochranelibrary.com/) – 2008 Issue 1 - no new records
- DARE (Database of Abstracts of Reviews of Effects) (CRD administration database) – 28 March 2008 – no new records
- HTA (Health Technology Assessment) Database (CRD administration database) – 28 March 2008 – no new records

Additional economics searching

Search on 29 January 2008
Retrieved 162 hits

MEDLINE In-process (Ovid Online – www.ovid.com/)
January 28 2008
Search on 29 January 2008
Retrieved 4 hits

1. (eq5d or eq 5d or euroqol or euro qol or euroqual or euro qual).ti,ab.
2. (hye or hyes or health$year$equivalent$or health utilit$).ti,ab.
3. rosser.ti,ab.
4. (standard gamble$or time trade off or time tradeoff or tto or willingness to pay).ti,ab.
5. (disutilities or disutility or daly or disability adjusted life).ti,ab.
6. quality-adjusted life years/
7. qwb$.ti,ab.
8. (quality of wellbeing or quality of well being).ti,ab.
9. preference based.ti,ab.
10. (state adj2 (value or values or valuing or valued)).ti,ab.
11. (multiattribute$health or multiattribute$health).ti,ab.
12. (health utilit$index or health utilit$indices).ti,ab.
13. (multiattribute$theor$or multiattribute$theor$or multiattribute$analys$or multiattribute$analys$).ti,ab.
14. classification of illness state$.ti,ab.
15. health state$utilit$.ti,ab.
16. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
17. (sf 6d or sf6d or short form 6d or short form 6d or sf six$or short form six$).ti,ab.
18. or/1–17
19. exp Angina Pectoris/
20. angina.ti,ab.
21. exp Heart Failure/
22. heart failure.ti,ab.
23. cardiac failure.ti,ab.
24. myocardial failure.ti,ab.
25. or/19–24
26. 18 and 25

EMBASE (Ovid Online – www.ovid.com/)
1980–2008 (week 4)
Searched on 29 January 2008
Retrieved 264 hits

1. (eq5d or eq 5d or euroqol or euro qol or euroqual or euro qual).ti,ab.
2. (hye or hyes or health$year$equivalent$or health utilit$).ti,ab.
3. rosser.ti,ab.
4. (standard gamble$or time trade off or time tradeoff or tto or willingness to pay).ti,ab.
5. (disutilities or disutility or daly or disability adjusted life).ti,ab.
6. quality-adjusted life year/
7. qwb$.ti,ab.
8. (quality of wellbeing or quality of well being).ti,ab.
9. preference based.ti,ab.
10. (state adj2 (value or values or valuing or valued)).ti,ab.
11. (multiattribute$health or multiattribute$health).ti,ab.
12. (health utilit$index or health utilit$indices).ti,ab.
13. (multiattribute$theor$or multiattribute$theor$or multiattribute$analys$or multiattribute$analys$).ti,ab.
14. classification of illness state$.ti,ab.
15. health state$utilit$.ti,ab.
16. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
17. (sf 6d or sf6d or short form 6d or short form 6d or sf six$or short form six$).ti,ab.
18. or/1–17
19. exp Angina Pectoris/
20. angina.ti,ab.
21. Heart Failure, Congestive/
22. heart failure.ti,ab.

23. cardiac failure.ti,ab.
24. myocardial failure.ti,ab.
25. or/19–24
26. 18 and 25
Appendix 2

Excluded studies
<table>
<thead>
<tr>
<th>Study</th>
<th>Inappropriate interventiona</th>
<th>Inappropriate participantsb</th>
<th>EECP clinical consortium</th>
<th>International EECP Patient Registry</th>
<th>Cardiomedics Registry</th>
<th>Other case series</th>
<th>Study in progress (authors contacted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akhtar et al., 2006</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Arora et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Arora et al., 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Bagger, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Bagger et al., 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Barsness et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Bonetti et al., 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Cleland, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Cohn and Lawson, 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Cohn et al., 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Cowie et al., 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Dockery et al., 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>El-Sakka et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>El-Sakka et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Fitzgerald et al., 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Fricchione et al., 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Gloth and Oken, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Guo et al., 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Hall, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Henrikson and Chandra-Strobos, 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Study</td>
<td>Inappropriate intervention</td>
<td>Inappropriate participants</td>
<td>Study design</td>
<td>Study in progress (authors contacted)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>-------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaluski et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kasliwal et al., 1996</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lakshmi et al., 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2000</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2005</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2006</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2007</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2000</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 1992</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 1996</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 1996</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 1995</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2001</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Inappropriate intervention</td>
<td>Inappropriate participants</td>
<td>EECP clinical consortium</td>
<td>International EECP Patient Registry</td>
<td>Cardiomedics Registry</td>
<td>Other case series</td>
<td>Study in progress (authors contacted)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
<td>------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Lawson et al., 2003</td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawson et al., 2005</td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levenson et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linnemeier et al., 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linnemeier et al., 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loh, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Loh et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Masuda et al., 2004</td>
<td></td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Masuda et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCullough et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCullough et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaels et al., 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaels et al., 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaels et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaels et al., 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaels et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Inappropriate intervention</td>
<td>Inappropriate participants</td>
<td>EECP clinical consortium</td>
<td>International EECP Patient Registry</td>
<td>Cardiomedics Registry</td>
<td>Other case series</td>
<td>Study in progress (authors contacted)</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------</td>
<td>---------------------------</td>
<td>--------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Michaels et al., 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Michaels et al., 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Moore, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Nichols et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Novo et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Ochoa et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Olsson, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Pettersson et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Rana et al., 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Saja et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Soran et al., 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Soran et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Soran et al., 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Soran et al., 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Springer et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Styx et al., 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Styx et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Sun, 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Tartaglia et al., 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Urano et al., 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Vijayaraghavan et al.,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Walker, 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>
## Reason for exclusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Inappropriate interventiona</th>
<th>Inappropriate participantsb</th>
<th>EECP clinical consortium</th>
<th>International EECP Patient Registry</th>
<th>Cardiomedics Registry</th>
<th>Other case series</th>
<th>Study in progress (authors contacted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisfogel et al., 2001130</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Werner et al., 2003131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Yavari and Montazeri, 2007132</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Yi et al., 1999133</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youcheng, 1991134</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Zheng, 1981135</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>Zheng et al., 1983136</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a The intervention was not EECP (35 hours, once or twice a day over 4–7 weeks) or the comparator was not usual care or placebo.

b The study participants did not have refractory angina and heart failure.

c The study design was not an RCT, a controlled clinical trial, a cohort with contemporaneous control group, or a case–control.
### Appendix 3

#### Quality assessment

<table>
<thead>
<tr>
<th>Assessment criteria</th>
<th>Study</th>
<th>Barsheshet et al., 2008</th>
<th>Holubkov et al., 2002</th>
<th>Shechter et al., 2003</th>
<th>Feldman et al., 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the method used to assign participants to treatment groups truly random?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>If non-randomised, describe how participants were allocated to treatment groups</td>
<td>NA</td>
<td>Patients were referred to the EECP programme. The control group consisted of age- and gender-matched patients who refused EECP</td>
<td>Comparison of two registries</td>
<td>The EECP group was recruited from an EECP program. Age- and gender-matched patients who refused EECP were the control group</td>
<td>NA</td>
</tr>
<tr>
<td>Was the treatment allocation concealed?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the treatment groups similar at baseline?</td>
<td>No</td>
<td>The EECP group had longer duration of angina and a higher proportion with previous MI</td>
<td>Yes</td>
<td>The EECP group had higher prevalence of several risk factors</td>
<td>Yes</td>
</tr>
<tr>
<td>If the above answer was no, was this taken into consideration in the analysis or study design?</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Did the analysis include an ITT analysis (i.e. were all participants included in the analysis, in the group to which they were allocated)?</td>
<td>Yes (for some outcomes)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>A partial ITT analysis – two participants who withdrew prior to first treatment were not included in the analysis</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Were appropriate methods used to account for missing data in the ITT analysis?</td>
<td></td>
<td>(Last observation carried forward)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment criteria</td>
<td>Arora et al., 199917</td>
<td>Barsheshet et al., 200818</td>
<td>Holubkov et al., 200219</td>
<td>Shechter et al., 200320</td>
<td>Feldman et al., 200621</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>-----------------------</td>
<td>----------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Was any of the outcome assessment blinded?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Staff responsible for baseline and follow-up assessment were blinded</td>
</tr>
<tr>
<td>Proportion of participants who did not complete the study</td>
<td>EECP: 13/72 (18%)</td>
<td>0% (none reported)</td>
<td>Unclear</td>
<td>0% (none reported)</td>
<td>EECP 22/93 (23.7%)</td>
</tr>
<tr>
<td></td>
<td>Control: 2/67 (3%)</td>
<td></td>
<td></td>
<td></td>
<td>Control 13/94 (13.8%)</td>
</tr>
<tr>
<td>NA, not applicable.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 4

Data extraction tables for clinical effectiveness review
<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Withdrawals</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td>List of outcomes</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td>reported and how</td>
</tr>
<tr>
<td>EECP</td>
<td></td>
<td></td>
<td>they were</td>
</tr>
<tr>
<td>35 1-hour</td>
<td>Number of</td>
<td>Number of</td>
<td>measured</td>
</tr>
<tr>
<td>sessions of</td>
<td>withdrawals</td>
<td>withdrawals</td>
<td>ETT</td>
</tr>
<tr>
<td>EECP could be</td>
<td>and losses</td>
<td>and losses</td>
<td>Exercise duration</td>
</tr>
<tr>
<td>given once or</td>
<td>to follow-up</td>
<td>to follow-up</td>
<td>(seconds) – time</td>
</tr>
<tr>
<td>twice a day.</td>
<td>EECP (n = 72</td>
<td>EECP (n = 13)</td>
<td>from the start of</td>
</tr>
<tr>
<td>Protocol-</td>
<td>; control n =</td>
<td>Prior to first</td>
<td>exercise to the</td>
</tr>
<tr>
<td>specified</td>
<td>67</td>
<td>treatment n = 1</td>
<td>beginning of the</td>
</tr>
<tr>
<td>applied was</td>
<td></td>
<td>Owing to</td>
<td>recovery period</td>
</tr>
<tr>
<td>300 mmHg</td>
<td></td>
<td>adverse event</td>
<td>Time to ≥ 1-mm ST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 9</td>
<td>segment depression(s) – the time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Owing to</td>
<td>from initiation of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other medical</td>
<td>exercise to the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>event n = 2</td>
<td>occurrence of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Owing to</td>
<td>horizontal or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>personal</td>
<td>down-sloping ST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reasons n = 1</td>
<td>segment depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ETT data</td>
<td>≥ 1 mm, 80 ms after</td>
</tr>
<tr>
<td></td>
<td></td>
<td>were</td>
<td>the J point,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>available</td>
<td>persisting for at</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 57 of 59</td>
<td>least three</td>
</tr>
<tr>
<td>Comparator</td>
<td></td>
<td>who completed</td>
<td>consecutive beats</td>
</tr>
<tr>
<td>35 hours of</td>
<td></td>
<td>the trial</td>
<td></td>
</tr>
<tr>
<td>inactive (sham)</td>
<td></td>
<td>(four</td>
<td></td>
</tr>
<tr>
<td>counterpulsation</td>
<td></td>
<td>protocol</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>violations,</td>
<td></td>
</tr>
<tr>
<td>sessions lasting</td>
<td></td>
<td>seven</td>
<td></td>
</tr>
<tr>
<td>1 hour could be</td>
<td></td>
<td>adverse event</td>
<td></td>
</tr>
<tr>
<td>given once or</td>
<td></td>
<td>event</td>
<td></td>
</tr>
<tr>
<td>twice a day.</td>
<td></td>
<td>withdrawals</td>
<td></td>
</tr>
<tr>
<td>Cuff pressure</td>
<td></td>
<td>and three</td>
<td></td>
</tr>
<tr>
<td>was 75 mmHg in</td>
<td></td>
<td>for personal</td>
<td></td>
</tr>
<tr>
<td>this group</td>
<td></td>
<td>reasons.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>these</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>withdrawals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>may already</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>be reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>above, as</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>data in the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>study flow</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>chart and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>text did not</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>tally</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>report</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>differences</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>between</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>participants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>that dropped</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>out and those</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>that did not</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes (specify)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes, for HRQoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>participants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>who supplied</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>QoL data</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>were</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>compared to</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>those who</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>had not. The</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>without QoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>data were</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>younger, more</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>had an MI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and had</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>higher CCS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>classification</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between 21 and 81 years old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS Classification I, II or III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented evidence of coronary artery disease (criteria specified)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have an exercise treadmill test positive for ischaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI or CABG in the preceding 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterisation in the preceding 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt congestive heart failure or a left ventricular ejection fraction less than or equal to 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant valvular heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure &gt; 180/100 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent pacemaker or implantable defibrillator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-bypassed left main stenosis &gt; 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Related papers: Arora et al., 2002 reports data on QoL, 12 months after treatment; conference proceedings – summary of QoL subgroup study
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>EECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe symptomatic peripheral vascular disease</td>
<td></td>
</tr>
<tr>
<td>History of varicosities, deep vein thrombosis, phlebitis or stasis ulcer, bleeding diathesis</td>
<td></td>
</tr>
<tr>
<td>Warfarin use with International Normalised Ratio &gt; 2.0</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering, or baseline electroencephalogram abnormalities that would interfere with interpretation of exercise ECG</td>
<td></td>
</tr>
<tr>
<td>Pregnant women and women of childbearing potential</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker: EECP 44 (62.0); control 36 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker: EECP 50 (70.4); control 51 (77.3)</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering agents: EECP 44 (62.0); control 33 (50.0)</td>
<td></td>
</tr>
<tr>
<td>NTG usage, mean (SE) EEC 0.47 (0.13); control 0.51 (0.15)</td>
<td></td>
</tr>
<tr>
<td>QoL</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Angina years, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>EECP 8.56 (7.88); control 4.5 (4.06), p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td></td>
</tr>
<tr>
<td>EECP n = 40 (56.3%); control n = 27 (40.9%), p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Previous CABG</td>
<td></td>
</tr>
<tr>
<td>EECP n = 33 (46.5%); control n = 25 (37.9%)</td>
<td></td>
</tr>
<tr>
<td>Previous percutaneous transluminal coronary angioplasty</td>
<td></td>
</tr>
<tr>
<td>EECP n = 27 (38.0%); control n = 22 (33.3%), p &gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>All baseline characteristics based on 71 and 66 participants for EECP and inactive EECP respectively</td>
<td></td>
</tr>
</tbody>
</table>

### Results

**Exercise duration, mean seconds (SE)**

EECP (n = 57): baseline 426 (20), post treatment 470 (20), p < 0.001; control (n = 58): baseline 432 (22), post treatment 464 (22), p < 0.03

*Adjusted mean (SE)*

EECP 42 (11); control 26 (12), between group p-value (using adjusted means): p < 0.31

**Exercise duration, time to ST segment depression(s), mean (SE)**

EECP (n = 56): baseline 337 (18), post treatment 379 (18), p < 0.002; control (n = 56): baseline 326 (21), post treatment 330 (20), p < 0.74

*Adjusted mean (SE)*

EECP 37 (11); control 4 (12). Between group p-value (using adjusted means): p = 0.01

**NYHA classification**: not applicable

**CCS classification**: not reported
Angina episodes

**Angina counts – ITT analysis, mean (SE?)**

EECP (n = 71): baseline 0.76 (0.15), post treatment 0.55 (0.27); control (n = 66): baseline 0.76 (0.13), post treatment 0.77 (0.22)

Adjusted mean (SE?): EECP –0.11 (0.21); control 0.13 (0.22). Between group p-value (using adjusted means), p < 0.09

**Angina counts – patients who received at least 34 sessions**

EECP: baseline 0.72 (0.14), post treatment 0.57 (0.38); control: baseline 0.77 (0.14), post treatment 0.76 (0.22). Between group p-value (using adjusted means), p < 0.035

It was unclear for some of the analysis whether SE or SD was being reported. We have made an assumption that the variance used is SE

---

% improvement (from baseline) – ITT analysis

EECP (n = 71): > 50% n = 32, 25–49% n = 1, 0–25% n = 33; control: (n = 66): > 50% n = 21, 25–49% n = 3, 0–25% n = 28

% worsening (from baseline)

EECP: 1–25% n = 0, 26–50% n = 0; 51–100% n = 2, 100% n = 3; control: 1–25% n = 2, 26–50% n = 2, 51–100% n = 4, 100% n = 6

p-value for between group differences < 0.05

% improvement (from baseline) – analysis of greater than or equal to 34 sessions

EECP (n = 57): > 50% n = 29, 25–49% n = 1, 0–25% n = 23; control: (n = 59) > 50% n = 19, 25–49% n = 2, 0–25% n = 24

% worsening (from baseline)

EECP: 1–25% n = 0, 26–50% n = 0, 51–100% n = 0, 100% n = 4; control: 1–25% n = 0, 26–50% n = 2, 51–100% n = 5, 100% n = 7

p-value for between group differences < 0.02

VO\textsubscript{2} related: not reported

---

QoL

(Magnitude of improvement or decline expressed in standard deviation units, baseline to end of treatment)

Number of evaluable patients n = 71: EECP n = 36; control n = 35. Relationship between evaluable status and treatment group assignment p = 0.99

Physical functioning: EECP (n = 36) 0.75, p < 0.05; control (n = 35) 0.4, p < 0.05

Role disability due to physical health: EECP (n = 33) 0.55, p < 0.01; control (n = 34) 0.2

Bodily pain: EECP (n = 36) 0.65, p < 0.01; control (n = 35) 0.35, p < 0.05

General health: EECP (n = 34) 0.25; control (n = 34) –0.01

Vitality: EECP (n = 35) 0.2; control (n = 34) 0.15

Social functioning: EECP (n = 36) 0.35, p < 0.05; control (n = 35) –0.1. Between group difference in change p < 0.05

Role disability due to emotional health: EECP (n = 35) 0.6, p < 0.01; control (n = 34), 0.01. Between group difference in change p < 0.05

Mental health: EECP (n = 35) 0.35, p < 0.05; control (n = 34) 0.3

QLI-HF (cardiac specific health and functioning): EECP (n = 36) 0.65, p < 0.01; control (n = 35) 0.4, p < 0.05

---

**TABLE 13** Arora et al., 1999.\textsuperscript{17} Related papers: Arora et al., 2002\textsuperscript{22} reports data on QoL, 12 months after treatment; conference proceedings – summary of QoL subgroup study (continued)
QoL
(Magnitude of improvement or decline expressed in standard deviation units, baseline to 1 year follow-up)

Physical functioning: EECP (n = 36) 0.6, p < 0.01; control (n = 35) 0.3, p < 0.05 RP (work)

Role disability due to physical health: EECP (n = 35) 0.6, p < 0.01; control (n = 35) 0.3

Bodily pain: EECP (n = 36) 0.5, p < 0.01; control (n = 35) 0.15. Between group difference in change p < 0.01

General health: EECP (n = 34) 0.25; control (n = 33) –0.05

Vitality: EECP (n = 36) 0.2; control (n = 33) 0.05

Social functioning: EECP (n = 36) 0.35 p < 0.05; control (n = 35) -0.1. Between group difference in change p < 0.05

Role disability due to emotional health: EECP (n = 36) 0.55, p < 0.01; control (n = 35) 0.15

Mental health: EECP (n = 36) 0.35, p < 0.05; control (n = 33) 0.2

QLI-HF (cardiac specific health and functioning): EECP (n = 36) 0.6, p < 0.01; control (n = 35) 0.2. Between group difference in change p < 0.01

Medication use
NTG usage, mean (SE?) (ITT analysis)
EECP: baseline 0.47 (0.13), post treatment 0.19 (0.07); control: baseline 0.51 (0.15), post treatment 0.45 (0.19)

Adjusted mean (SE?): EECP –0.32 (0.12); control -0.10 (0.12). Between group p-value (using adjusted means) p > 0.1

NTG usage, mean (SE?) (patients who completed at least 34 sessions)
EECP: baseline 0.39 (0.11), post treatment 0.12 (0.04); control: baseline 0.56 (0.17), post treatment 0.43 (0.21). Between group p-value (using adjusted means) p > 0.1

It was unclear for some of the analyses whether SE or SD was being reported. We have made an assumption that the variance used is SE

Adverse events (EECP n = 71; control n = 66)
Patients with adverse experiences: EECP n = 39 (54.9%); control n = 17 (25.8%) p < 0.001

Adverse experiences: non-device related (EECP, control)
Viral syndrome 1, 0; anxiety 2, 0; dizziness 3, 1; tinnitus 1, 0; gastrointestinal disturbances 1, 1; headache 1, 0; blood pressure change 1, 1; epistaxis 2, 0; angina 1, 1; other chest pain 7, 3; atrioventricular arrhythmia 9, 3; heart rate change (sinusal) 0, 3; respiratory 4, 2
Total 33, 15, p < 0.005

Adverse experiences: device related (EECP, control)
Paraesthesia 2, 1; oedema, swelling 2, 0; skin abrasion, bruise, blister 13, 2; pain (legs, back) 20, 7
Total 37, 10, p < 0.001

Leg discomfort reported in 11.6% (SE? 22.7) of EECP sessions and 4.9% (SE? 18.7) of control sessions. Owing to a typo, it is unclear which group had the greater percentage of leg discomfort – we have made the assumption it was the EECP group

Summary of other outcomes: not applicable
Details of subgroup analysis: not applicable
Subgroup analysis results: not applicable

ETT, exercise treadmill test.
<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Withdrawals</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-randomised controlled study</td>
<td>Number allocated to each group</td>
<td>Number of withdrawals and losses to follow-up</td>
<td>List of outcomes reported and how they were measured</td>
</tr>
<tr>
<td>Intervention</td>
<td>EECP: n = 15; control n = 10</td>
<td>None reported</td>
<td>CCS angina class</td>
</tr>
<tr>
<td>ECEP</td>
<td>Age (mean SD)</td>
<td>Did study report differences between participants that dropped out and those that did not?</td>
<td>Reported but not extracted</td>
</tr>
<tr>
<td>35 hours of EECP over 7 weeks, i.e. 1 hour per day, 5 days per week</td>
<td>EECP 69.8 (11.2); control 69.3 (9.6)</td>
<td>Not applicable</td>
<td>Number and colony-forming capacity of EPCs – changes in circulating EPCs were measured using flow activated cell sorter analysis and by counting EPC-CFUs (colony forming units)</td>
</tr>
<tr>
<td>Details of any other therapy</td>
<td>Sex (% male)</td>
<td>Endothelial function – percentage change in flow-mediated dilation after cuff deflation</td>
<td></td>
</tr>
<tr>
<td>All medications, diet and interventions were constant over the 10-week period after the participants were recruited to the study</td>
<td>EECP 12 (80); control 10 (100)</td>
<td>Endothelial dysfunction – asymmetric dimethylarginine, vascular endothelial growth factor and c-reactive protein levels were measured)</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care (not specified)</td>
<td>Condition being treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Details of any other therapy</td>
<td>Stable angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All medications, diet and interventions were constant over the 10-week period after the participants were recruited to the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Baseline clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men and women 40–90 years old</td>
<td>VO$_2$ related: not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic coronary artery disease (CAD) documented by previous angiography (&gt; 70% stenosis in any coronary artery)</td>
<td>NYHA classification: not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS classification II–IV</td>
<td>CCS classification, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise duration: not reported</td>
<td>EECP: Class II 2 (13.3); Class III 7 (46.6); Class IV: 6 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina episodes: not reported</td>
<td>Control: Class II 2 (20); Class III 5 (50); Class IV 3 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication use, n (%)</td>
<td>Exercise duration: not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Aspirin: EECP 14 (93.3); control: 9 (90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction in previous 3 months</td>
<td>Beta-blockers: EECP 12 (80); control 7 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>Statins: EECP 13 (86.6); control 10 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension &gt; 180/110 mmHg</td>
<td>Long acting nitrates: EECP 9 (60); control 5 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation or ventricular premature beats that would interfere with EECP triggering</td>
<td>Diuretics: EECP 6 (40); control 4 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACE/ARB EECP 9 (60); control 7 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>QoL: not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 14 Barsheshet et al., 2008**

*EECP n = 15; control n = 10*
<table>
<thead>
<tr>
<th>Clinically evident peripheral vascular disease</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>History of MI, n (%)</td>
</tr>
<tr>
<td>Phlebitis and haemorrhagic diathesis</td>
<td>EECP 12 (80); control 9 (90)</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>Previous revascularisation (PTCA and/or CABG), n (%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>EECP 14 (93.3); control 10 (100)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td></td>
</tr>
</tbody>
</table>

### Results

- **Exercise duration:** not reported
- **NYHA classification:** not applicable
- **CCS classification:** CCS changed from a categorical to a continuous scale, median (interquartile range)
  - EECP: baseline 3.0 (3.0–4.0), post treatment: 2.0 (2.0–3.0), \( p < 0.001 \); control: baseline 3.0 (2.5–4.0); post treatment: 3.0 (2.0–3.5), \( p = 0.50 \)
- **Angina episodes:** not reported
- **\( \text{VO}_2 \) related:** not reported
- **QoL:** not reported
- **Medication use:** not reported
- **Adverse events:** not reported
- **Summary of other outcomes:** not applicable
- **Details of subgroup analysis:** not applicable

EPC, endothelial progenitor cell.
## Table 15: Feldman et al., 2006. 
Related papers: Abbottsmith et al., 2006 report on an additional subgroup analysis of older people; Feldman et al., 2005 give details of PEECH trial methodology

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Withdrawals</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td><strong>Number allocated to each group</strong></td>
<td><strong>Number of withdrawals and losses to follow-up</strong></td>
<td><strong>List of outcomes reported and how they were measured</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>EECP n = 93; control n = 94</td>
<td>EECP n = 22 (23.7%)</td>
<td>Exercise duration – percentage of patients that showed an increase in duration of 60 seconds or more</td>
</tr>
<tr>
<td>EECP</td>
<td>Age [mean (SD)]</td>
<td>Adverse event: 11</td>
<td>Peak VO$_2$ – percentage of patients with an increase in peak VO$_2$ ≥ 1.25 ml/kg/minute from baseline at 6 months’ follow-up</td>
</tr>
<tr>
<td>35 1-hour sessions of EECP over 7–8 weeks. Protocol-specified applied pressure was 300 mmHg, and was reached within 5 minutes of treatment initiation</td>
<td>EECP 62.4 (11.7); control 63.0 (10.4)</td>
<td>Protocol violation: 2</td>
<td>Change in peak VO$_2$</td>
</tr>
<tr>
<td><strong>Details of any other therapy</strong></td>
<td>Sex (% male)</td>
<td>Refused assignment: 2</td>
<td>Change in exercise duration</td>
</tr>
<tr>
<td>Continued pharmacotherapy (PT)</td>
<td>EECP 77.4%; control 75.5%</td>
<td>Non-compliance: 1</td>
<td>Change in ventilatory equivalent for carbon dioxide</td>
</tr>
<tr>
<td>Comparator</td>
<td>Race</td>
<td>Participant’s decision: 5</td>
<td>Change in respiratory exchange ratio</td>
</tr>
<tr>
<td>Continued pharmacotherapy</td>
<td>Caucasian: EECP n = 76 (81.7%); control n = 75 (79.8%)</td>
<td>Loss to follow-up: 2</td>
<td>Change in Borg Score</td>
</tr>
<tr>
<td>For both groups, patients were receiving heart failure therapy in compliance with the Practice Guidelines of the Heart Failure Society of America</td>
<td>Condition being treated</td>
<td>Other: 4</td>
<td>Change in ventilatory response ([l/minute])</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Heart failure</td>
<td>Control n = 13 (13.8%)</td>
<td>Change in NYHA functional class</td>
</tr>
<tr>
<td>Symptomatic mild to moderate heart failure (NYHA class II – III) secondary to either ischaemic or non-ischaemic cardiomyopathy and a LVEF ≤ 35%</td>
<td>Baseline clinical characteristics</td>
<td>Protocol violation: 2</td>
<td>Change in QoL (Minnesota Living with Heart Failure Questionnaire)</td>
</tr>
<tr>
<td>Clinically stable</td>
<td>VO$_2$ related</td>
<td>Refused assignment: 1</td>
<td>Adverse events (an independent clinical end-points committee classified adverse events)</td>
</tr>
<tr>
<td>Minimal or no oedema</td>
<td>Peak VO$_2$, ml/kg/minute, mean (SE)</td>
<td>Non-compliance: 0</td>
<td></td>
</tr>
<tr>
<td>Be receiving heart failure therapy in compliance with the Practice Guidelines of the Heart Failure Society of America before enrolling</td>
<td>EECP 14.7 (0.4); control 14.1 (0.4)</td>
<td>Participant’s decision: 6</td>
<td></td>
</tr>
<tr>
<td>Before enrolling be taking an ACE inhibitor or an angiotensin-receptor blocker and beta-blocker for at least 1 and 3 months respectively, unless these drugs are not tolerated</td>
<td>(Based on 80 and 84 patients respectively)</td>
<td>Loss to follow-up: 1 Other: 1</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>NYHA classification, n (%)</td>
<td>Additional losses to follow-up</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome in the 6 weeks prior to enrolment</td>
<td>Class II: EECP 60 (64.5%); control 62 (66%)</td>
<td>EECP: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class III: EECP 33 (35.5%); control 32 (34.0%)</td>
<td>Pharmacotherapy: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercise duration, seconds, mean (SE)</td>
<td>Did study report differences between participants that dropped out and those that did not?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EECP 610.6 (27.8); control 570.9 (26.1)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Based on 80 and 84 patients respectively)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors, n (%): EECP 70 (75.3); control 73 (77.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enalapril daily dose equivalent (mg), mean (SD): EECP 11.8 (10.1); control 13.5 (9.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median: EECP 10; control 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin-receptor blockers, n (%): EECP 18 (19.4); control 18 (19.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Losartan daily dose equivalent (mg), mean (SD): EECP 63.2 (42.0); control 60.5 (38.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-bypassed left main coronary with a luminal stenosis ≥ 50%
CABG in previous 3 months, PCI in previous 6 months or cardiac catheterisation in previous 2 weeks
Arrhythmias that could interfere with EECP
Chronic obstructive pulmonary disease (COPD) with forced expiratory volume of 1 second (FEV1) ≤ 1.5L
Clinically significant valvular heart disease, acute myocarditis
History of deep vein thrombosis, phlebitis, stasis ulcer, pulmonary embolism or aortic aneurysm
Uncontrolled hypertension

<table>
<thead>
<tr>
<th>Methodology</th>
<th>List of outcomes reported and how they were measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% male)</td>
<td>Results</td>
</tr>
<tr>
<td>Number of withdrawals and losses</td>
<td>Exercise duration [mean change in exercise duration from baseline(s) (SE)]</td>
</tr>
<tr>
<td></td>
<td>1-week follow-up: EECP (n = 77) 26.4 (12.2); control (n = 78) –5.5 (11.7), p = 0.010</td>
</tr>
<tr>
<td></td>
<td>3-month follow-up: EECP (n = 78) 34.5 (13.9); control (n = 82) –7.0 (12.7), p = 0.014</td>
</tr>
<tr>
<td></td>
<td>6-month follow-up: EECP (n = 79) 24.7 (15.2); control (n = 83) –9.9 (13.2), p = 0.013</td>
</tr>
<tr>
<td></td>
<td>Exercise duration (percentage of patients with at least a 60-second increase in exercise duration from baseline to 6 months’ follow-up)</td>
</tr>
<tr>
<td></td>
<td>EECP 35.4%; control 25.3%, p = 0.016</td>
</tr>
<tr>
<td></td>
<td>NYHA classification (% patients with an improvement in NYHA class)</td>
</tr>
<tr>
<td></td>
<td>1-week follow-up: EECP 33.3%; control 11.4%, p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>3-month follow-up: EECP 31.6%; control 12.2%, p &lt; 0.02</td>
</tr>
<tr>
<td></td>
<td>6-month follow-up: EECP 31.3%; control 14.3, p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>CCS classification: not applicable</td>
</tr>
<tr>
<td></td>
<td>Angina episodes: not applicable</td>
</tr>
<tr>
<td></td>
<td>VO₂ related [mean change in peak VO₂ (ml/kg/minute) (SE)]</td>
</tr>
<tr>
<td></td>
<td>1-week follow-up: EECP (n = 77) 0.1 (0.3); control (n = 78) –0.4 (0.3), p = 0.071</td>
</tr>
<tr>
<td></td>
<td>3-month follow-up: EECP (n = 78) 0.2 (0.3); control (n = 82) –0.4 (0.3), p = 0.119</td>
</tr>
<tr>
<td></td>
<td>6-month follow-up: EECP (n = 79) –0.3 (0.3); control (n = 83) –0.6 (0.3), p = 0.315</td>
</tr>
<tr>
<td></td>
<td>VO₂ related (% patients with a peak VO₂ increase ≥ 1.25 ml/kg/minute from baseline to 6 months’ follow-up)</td>
</tr>
<tr>
<td></td>
<td>EECP 22.8%; control 24.1%, p = 0.698</td>
</tr>
</tbody>
</table>

Beta-blockers, n (%): EECP 79 (84.9%); control 81 (86.2)
Carvedilol daily dose equivalent (mg), mean (SD): EECP 39.4 (29.7); control 39.7 (30.1)
Median: EECP 25; control 25
QoL: baseline not reported

Other
Aetiology, ischaemic, n (%): EECP 66 (68.8%); control 66 (70.2%)
Heart rate, beats per min (SD): EECP 70.7 (11.2); control 70.6 (12.0)
Blood pressure mmHg (SD): systolic: EECP 116.7 (17.7); control 114.8 (18.4); diastolic: EECP 70.9 (10.2); control 70.8 (10.8)
LVEF mean % (SD): EECP 25.9% (6.1); control 26.7% (6.5)

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
QoL (mean change in QoL score (CI) using Minnesota Living with Heart Failure Questionnaire) estimated from Figure 1
1-week follow-up: EECP –8.8 (–7 to –10.9); control –3.5 (–1.5 to –5), \( p = 0.01 \)
3-month follow-up: EECP –7.2 (–4.7 to –9.5); control –2.8 (–1 to –4.6), \( p = 0.01 \)
6-month follow-up: EECP –3.5 (–1.3 to –6); control –2.8 (–0.5 to –4.5), \( p = 0.32 \)
Medication use: not reported

**Adverse events**

Percentage of patients discontinuing due to an adverse experience
EECP 11.8; control 3.2

*Discontinuation due to adverse event during treatment period*
EECP: sciatica \( n = 1 \), leg pain \( n = 1 \), arrhythmia \( n = 2 \), non-Q wave MI not attributable to therapy \( n = 1 \); control: death \( n = 2 \)

*Discontinuation due to adverse events in the follow-up period*
EECP: worsening heart failure (WHF) \( n = 4 \), biventricular pacemaker implantation \( n = 1 \), worsening lung cancer \( n = 1 \), control: atrioventricular block \( n = 1 \)

**Serious adverse events (SAE)**

Percentage of patients with SAEs: EECP \( n = 27 \) (30.3%); control \( n = 26 \) (29.5%)

*During treatment period*
EECP: SAEs \( n = 7 \) (7.9%); related to treatment: WHF \( n = 1 \), pulmonary embolism \( n = 1 \); control: SAEs \( n = 8 \) (9.1%); related to treatment: WHF \( n = 0 \), pulmonary embolism \( n = 0 \)

*During follow-up*
EECP: SAEs \( n = 21 \) (23.6%); related to treatment: WHF \( n = 0 \), deep vein thrombosis \( n = 1 \); control: SAEs \( n = 23 \) (26.1%); related to treatment: WHF \( n = 1 \); deep vein thrombosis \( n = 0 \)
(There was a discrepancy in the paper between the total number of participants with SAE and the number of SAEs during treatment plus during follow-up)

**Pre-defined clinical events**
EECP: \( n = 89 \)
WHF requiring IV therapy \( n = 8 \) (9%); WHF with no IV \( n = 8 \) (1.1%) (as stated in paper but looks like a typo); acute coronary syndrome (ACS) \( n = 1 \) (1.1%); MI \( n = 1 \) (4.5%); cardiovascular death \( n = 0 \)
Control \( n = 88 \); WHF with IV \( n = 12 \) (13.6%); WHF with no IV \( n = 4 \) (2.3%); ACS \( n = 0 \) (0%); MI \( n = 0 \) (0%); cardiovascular death \( n = 2 \) (2.3%)

**Summary of other outcomes**
Ventilatory equivalent for carbon dioxide (VE/\( \text{VCO}_2 \)) – no change at any time point (data not presented)
There was no significant difference at baseline or any follow-up time points between groups in respiratory exchange ratio (RER) or Borg score (overall median = 17)
There was a statistically significant difference in ventilatory response (change in VE l/min) between groups at 1-week and 3-month follow-up, but not at 6 months
Subgroup analysis results

Subgroup 1: Patients with ischaemic versus non-ischaemic dilated cardiomyopathy

Mean change in exercise duration, (seconds) (SE): 1-week follow-up
EECP: ischaemic (n = 53) 24.6 (15.7), non-ischaemic (n = 24) 30.2 (18.3); control: ischaemic (n = 54) –16.7 (14.2), non-ischaemic (n = 24) 19.9 (20.3)
Ischaemic p = 0.007; non-ischaemic p = 0.836

Mean change in exercise duration, (seconds) (SE): 3-month follow-up
EECP: ischaemic (n = 54) 34.2 (17.2), non-ischaemic (n = 24) 35.4 (23.8); control: ischaemic (n = 57) –17.3 (13.1), non-ischaemic (n = 25) 16.7 (28.9)
Ischaemic p = 0.017; non-ischaemic p = 0.741

Mean change in exercise duration, (seconds) (SE): 6-month follow-up
EECP: ischaemic (n = 54) 20.6 (18.5), non-ischaemic (n = 25) 33.5 (26.8); control: ischaemic (n = 57) –25.8 (13.9), non-ischaemic (n = 26) 24.7 (28.3)
Ischaemic p = 0.010; non-ischaemic p = 0.724

Increase in NYHA classification
1-week follow-up: EECP 37%; control 12.7%, p = 0.004
3-month follow-up: EECP 34.5%; control 12.3%, p = 0.025
6-month follow-up: EECP 36.4%; control 15.5%, p = 0.026

Change in peak VO\textsubscript{2} (ml/kg/minute) (SE): 1-week follow-up
EECP: ischaemic (n = 53) 0.2 (0.4), non-ischaemic (n = 24) –0.2 (0.5); control: ischaemic (n = 54) –0.7 (0.4) non-ischaemic (n = 24) –0.4 (0.5)
Ischaemic p = 0.008; non-ischaemic p = 0.987

Change in peak VO\textsubscript{2} (ml/kg/minute) (SE): 3-month follow-up
EECP: ischaemic (n = 54) 0.0 (0.4) non-ischaemic (n = 24) 0.6 (0.5); control: ischaemic (n = 57) –0.4 (0.3); non-ischaemic (n = 25) –0.2 (0.8)
ischaemic p = 0.122; non-ischaemic p = 0.437

Change in peak VO\textsubscript{2} (ml/kg/minute) (SE): 6-month follow-up
EECP: ischaemic (n = 54) –0.4 (0.3) non-ischaemic (n = 25) –0.3 (0.5); control: ischaemic (n = 57) –0.9 (0.3) non-ischaemic (n = 26) 0.2 (0.6)
ischaemic p = 0.115; non-ischaemic p = 0.935

QoL
The only significant improvement was in the ischaemic group at 3 months’ follow-up: EECP –6.5 (3.2); PT –1.5 (2.1), p = 0.046
Subgroup analysis results

Subgroup 2: Older patients

There were no significant differences at baseline between the subgroup and overall population.

Exercise duration – mean change in exercise duration, seconds (variance not reported)

<table>
<thead>
<tr>
<th>Time</th>
<th>EECP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>23.0</td>
<td>3.4</td>
<td>0.07</td>
</tr>
<tr>
<td>3 months</td>
<td>52.2</td>
<td>-19.1</td>
<td>0.004</td>
</tr>
<tr>
<td>6 months</td>
<td>30.0</td>
<td>-22.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Exercise duration – increase in exercise duration ≥ 60 seconds from baseline to 6 months’ follow-up

<table>
<thead>
<tr>
<th></th>
<th>EECP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35.1</td>
<td>25%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Improvement in NYHA classification

<table>
<thead>
<tr>
<th>Time</th>
<th>EECP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>35.1%</td>
<td>9.8%</td>
<td>0.042</td>
</tr>
<tr>
<td>3 months</td>
<td>40.5%</td>
<td>9.1%</td>
<td>0.046</td>
</tr>
<tr>
<td>6 months</td>
<td>37.8%</td>
<td>15.9%</td>
<td>p-value not significant</td>
</tr>
</tbody>
</table>

Peak VO₂ – increase in peak VO₂ ≥ 1.25 ml/kg/minute from baseline to 6-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>EECP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29.7</td>
<td>11.4</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Mean change in peak VO₂ (from baseline, ml/kg/minute) (variance not reported)

<table>
<thead>
<tr>
<th>Time</th>
<th>EECP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>-0.1</td>
<td>-0.8</td>
<td>0.09</td>
</tr>
<tr>
<td>3 months</td>
<td>0.3</td>
<td>-1.1</td>
<td>0.02</td>
</tr>
<tr>
<td>6 months</td>
<td>-0.2</td>
<td>-1.1</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

QoL

There was no statistically significant difference in Minnesota Living with Heart Failure Questionnaire score between EECP and PT within the 65 or older subgroup at any time point (data not reported).

Adverse events

Adverse events were consistent with those in the overall study population, i.e. non-serious adverse events related to skin and musculoskeletal experience were more frequent in the EECP group.

Serious adverse events

<table>
<thead>
<tr>
<th></th>
<th>EECP</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (29.3%)</td>
<td>16 (36.4%)</td>
<td></td>
</tr>
</tbody>
</table>

1 serious adverse event was defined as definitely related to EECP (WHF in a 72-year-old man with ischaemic heart failure).

Events adjudicated by the PEECH committee occurred at a similar frequency in both study groups.
**TABLE 16 Holubkov et al., 2002**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Withdrawals</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-randomised controlled study</td>
<td>Number allocated to each group</td>
<td>Number of withdrawals and losses to follow-up</td>
<td>List of outcomes reported and how they were measured</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td>Loss to follow-up unclear</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>EECPer hour of treatment per day, 5 or 6 days per week with a minimum total of 35 hours</td>
<td>EECPer 323; control 448</td>
<td>Patients alive and contacted at follow-up:</td>
<td>Self-reported exertional angina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EECPer 65.7 (10.5); control 64.5 (11.6)</td>
<td>CCS classification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex [mean (SD)]</td>
<td>Medication use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EECPer 79.9; control 72.3, p &lt; 0.05</td>
<td>PCI during follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race: not reported</td>
<td>Repeat EECPer (EECP group only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition being treated</td>
<td>With the exception of mortality, outcomes were based on phone interview or by mail</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stable angina</td>
<td></td>
</tr>
<tr>
<td>Details of any other therapy</td>
<td></td>
<td>Baseline clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>None reported</td>
<td></td>
<td>VO2 related: not reported</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td></td>
<td>NYHA classification: not applicable</td>
<td></td>
</tr>
<tr>
<td>Elective PCI</td>
<td></td>
<td>CCS classification</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EECPer Class I 9.6%; Class II 26.0%; Class III 47.1%; Class IV 17.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: Class I 5.3%; Class II 41.4%; Class III 48.3%; Class IV 5.1%, p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Details of any other therapy</td>
<td></td>
<td>Exercise duration: not reported</td>
<td></td>
</tr>
<tr>
<td>None reported</td>
<td></td>
<td>Angina episodes: not reported</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td></td>
<td>Medication use: not reported</td>
<td></td>
</tr>
<tr>
<td>IEPR: all consecutive patients undergoing at least 1 hour of EECPer treatment with no clinical or other exclusions. Patients were included in this analysis if they had stable exertional angina and were classified as PCI candidates at the time of first EECPer treatment (14.8% of entire cohort)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Heart, Lung and Blood Institute Dynamic Registry of Coronary Interventions (Dynamic Registry): consecutive patients (with no exclusion criteria) undergoing insertion of a guide catheter as the first intended step of PCI. Patients were included in this analysis if they had undergone elective PCI for stable symptoms without myocardial infarction in the previous 30 days (23.2% of entire cohort)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

Exercise duration: not reported
NYHA classification: not applicable

CCS classification
EECP (n = 251): Class I, 22.0%; Class II, 18.8%; Class III, 11.8%; Class IV/unstable, 3.7%
Control (n = 422): Class I, 5.1%; Class II, 12.1%; Class III, 5.1%; Class IV/unstable, 4.4%, p = 0.02 for prevalence of Class III or IV/unstable angina
(Note: due to differences in how the two registries classified unstable angina, stable Class IV and unstable angina were treated as a single category)

Angina episodes (no angina)
EECP (n = 251): 43.7%; control (n = 422): 73.4%, p < 0.001
VO2 related: not reported
QoL: not reported

Medication use
Beta-blockers: EECP 53.8%; control 54.7%
Calcium channel blockers: EECP 50.6%; control 33.7%, p < 0.001
Long-acting nitrates: EECP 53.0%; control 30.3%, p < 0.001
ACE inhibitors: EECP 26.7%; control 28.0%
Angiotensin-receptor blockers: EECP 5.6%; control 1.9%, p < 0.01
Short-acting nitroglycerin: EECP 43.3%; control 82.2%, p < 0.001

Adverse events: not reported

Summary of other outcomes
1-year all-cause mortality: EECP 98.7% survival, mortality 1.3% (95% CI 0.5–3.5%); control 96.8% survival, mortality 3.2% (95% CI 1.9–5.4%) (not significant based on log-rank test)
PCI during follow-up: control 17.2% (95% CI 14.0–21.1%); EECP 6.3% (95% CI 4.0–9.9%)
Repeat EECP: EECP 9.1% (95% CI 6.2–13.0%)

Details of subgroup analysis
1-year angina CCS classification reported by baseline classification; subgroup analysis results: not extracted

Additional comments
85.8% of 323 patients treated with EECP completed a full course of treatment
92.1% of patients treated with PCI had a successful initial procedure (i.e. reduction of stenosis in all attempted lesions of at least 20% to a final stenosis of 50%, without occurrence of death, MI or emergency CABG during post-PCI hospitalisation
<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Withdrawals</th>
<th>Outcomes assessed</th>
</tr>
</thead>
</table>
| Non-randomised controlled study| Number allocated to each group  
EECP: n = 20; control n = 20  
Age [mean (SD)]  
EECP: 68 (11); control 67 (12)  
Sex (% male)  
EECP: 15 (75%); control 17 (85%)  
Race: not reported  
Condition being treated  
Stable angina | Number of withdrawals and losses to follow-up  
None | List of outcomes reported and how they were measured  
Use of nitroglycerin tablets during the preceding 7 days (mean sublingual nitrate consumption per day)  
CCS classification  
Adverse experiences – reported at each EECP session  
Flow-mediated dilation (%) and NTG-induced non-endothelium dependent vasodilatation (%) – measured using high resolution ultrasound |
| Intervention                   |  
EECP                                                                 | 35 hours over 7 weeks. Treatment sessions lasted for 1 hour, 5 days each week |  |
| Details of any other therapy   | Regular medications were continued and usual diet was maintained throughout                                                                                                                             |  |
| Comparator                     | Details not provided                                                                                                                                                                                      |  |
| Details of any other therapy   | Regular medications were continued and usual diet maintained throughout                                                                                                                                |  |
| Inclusion criteria             | Men and women > 20 years old with coronary artery disease documented by previous myocardial infarction, coronary artery bypass surgery or coronary angiography or angioplasty  
CCS classification III or IV determined by specific criteria |  |
| Exclusion criteria             | Unstable angina  
Congestive heart failure  
New York Heart Association > Class II  
Aortic regurgitation  
Valvular heart disease  
Acute MI < 3 months  
Left main stenosis > 50%  
Systemic hypertension > 180/110 mmHg  
Permanent pacemaker  
Atrial fibrillation or ventricular premature beats that would interfere with triggering EECP |  |
| Baseline clinical characteristics| VO$_2$ related: not reported  
NYHA classification: not applicable  
CCS classification, n (%)  
EECP: Class III 5 (25%); Class IV 15 (75%)  
Control: Class III 6 (30%); Class IV 14 (70%)  
Exercise duration: not reported  
Medication use, n (%)  
Beta-receptor antagonist: EECP 14 (70%); control 13 (65%)  
Calcium antagonists: EECP 9 (45%); control 7 (35%)  
Diuretics (lasix): EECP 4 (20%); control 5 (25%)  
Aspirin: EECP 19 (95%); control 19 (95%)  
Long-acting nitrates: EECP 16 (80%); control 17 (85%)  
ACE inhibitors: EECP 13 (65%); control 12 (60)  
Lipid-lowering agents: EECP 15 (75%); control 16 (80%)  
QoL: not reported |  |
<table>
<thead>
<tr>
<th>Clinically evident peripheral vascular disease</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>Body mass index (kg/m^2), mean (SD): EECp 26 (4); control 25 (7)</td>
</tr>
<tr>
<td>Phlebitis and haemorrhagic diathesis</td>
<td>Systemic hypertension, n (%): EECp 10 (50); control 7 (35)</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>Previous MI, n (%): EECp 14 (70); control 13 (65)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Previous coronary angioplasty, n (%): EECp 12 (60); control 13 (60)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>Previous coronary bypass, n (%): EECp 10 (50); control 11 (55)</td>
</tr>
<tr>
<td>History of drug or alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

**Exercise duration:** not applicable

**NYHA classification:** not applicable

**CCS classification**

Mean CCS angina class (SD) from baseline to post treatment (CCS changed from a categorical to a continuous scale)

EECP: baseline 3.5 (0.5), post-treatment 1.9 (0.3), \( p < 0.0001 \); control: baseline 3.3 (0.6), post treatment 3.5 (0.5), \( p = 0.89 \)

**Angina class at the end of the study, n (%):**

EECP: Class I 1 (5%), Class II 17 (85%), Class III 2 (10%), CCS Class IV 0; control data not reported

**Angina episodes:** not applicable

**VO₂ related:** not applicable

**QoL:** not reported

**Medication use [mean nitrate tablet consumption per day (SD) from baseline to post treatment]**

EECP: baseline 4.2 (2.7), post treatment 0.4 (0.5), \( p < 0.001 \); control: baseline 4.5 (2.3), post treatment 4.4 (2.6), \( p = 0.87 \)

**Adverse events**

The authors stated there were no serious adverse effects throughout the study

**Summary of other outcomes:** not applicable

**Details of subgroup analysis:** not applicable

**Subgroup analysis results:** not applicable
Appendix 5
Details of quality assessment for economic studies

<table>
<thead>
<tr>
<th>Study question</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Costs and effects examined</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2. Alternatives compared</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3. The viewpoint/perspective of the analysis is clearly stated (e.g. NHS, society)</td>
<td>Yes US payer’s perspective</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selection of alternatives</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4. All relevant alternatives are compared (including do nothing, if applicable)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5. The alternatives being compared are clearly described (who did what, to whom, where and how often?)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6. The rationale for choosing the alternative programmes or interventions compared is stated</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Form of evaluation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7. The choice of form of economic evaluation is justified in relation to the questions addressed</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effectiveness data</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>10. Effectiveness data from RCT or review of RCTs</td>
<td>No</td>
<td>Effectiveness data derived from registry data and observational studies. No RCT data were available for the alternatives being compared</td>
</tr>
<tr>
<td>11. Potential biases identified (especially if data are not from RCTs)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td>NA</td>
<td>No formal synthesis was undertaken</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>13. All the important and relevant resource use is included</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>14. All the important and relevant resource use is measured accurately (with methodology)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>15. Appropriate unit costs estimated (with methodology)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>16. Unit costs reported separately from resource use data</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>17. Productivity costs treated separately from other costs</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion</td>
<td>Yes 2004 US dollars</td>
<td>2004 US dollars</td>
</tr>
<tr>
<td>Benefit measurement and valuation</td>
<td>Manufacturer’s study&lt;sup&gt;24&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>19. The primary outcome measure(s) for the economic evaluation are clearly stated</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>20. Methods to value health states and other benefits are stated</td>
<td>No</td>
<td>No health states were valued</td>
</tr>
<tr>
<td>21. Details of the individuals from whom valuations were obtained are given</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decision modelling</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>22. Details of any decision model used are given (e.g. decision tree, Markov model)</td>
<td>Yes</td>
</tr>
<tr>
<td>23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified</td>
<td>Yes</td>
</tr>
<tr>
<td>24. All model outputs described adequately</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discounting</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Discount rate used for both costs and benefits</td>
<td>Unclear</td>
</tr>
<tr>
<td>26. Do discount rates accord with NHS guidance?</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allowance for uncertainty</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>27. Details of statistical tests and confidence intervals are given for stochastic data</td>
<td>NA</td>
</tr>
<tr>
<td>28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)</td>
<td>NA</td>
</tr>
<tr>
<td>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)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stochastic analysis of decision models</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30. Are all appropriate input parameters included with uncertainty?</td>
<td>No</td>
</tr>
<tr>
<td>31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?</td>
<td>No</td>
</tr>
<tr>
<td>32. Are the probability distributions adequately detailed and appropriate?</td>
<td>No</td>
</tr>
<tr>
<td>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)</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deterministic analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)</td>
<td>Yes</td>
</tr>
<tr>
<td>35. The choice of variables for sensitivity analysis is justified</td>
<td>Yes</td>
</tr>
<tr>
<td>36. The ranges over which the variables are varied are stated</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presentation of results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>37. Incremental analysis is reported using appropriate decision rules</td>
<td>Yes</td>
</tr>
<tr>
<td>38. Major outcomes are presented in a disaggregated as well as an aggregated form</td>
<td>Yes</td>
</tr>
<tr>
<td>39. Applicable to the NHS setting</td>
<td>No</td>
</tr>
</tbody>
</table>

---

NA, not applicable; No, item not adequately addressed; NS, not stated; Unclear, not enough information; Yes, item adequately addressed.
Appendix 6

Assumption of linearity in the economic model

The computational requirements for partial EVPI and EVSI can be simplified if the model has either a linear or a multilinear relationship between the parameters and the expected costs and outcomes. Although the economic model presented in Chapter 3, Decision model, is nonlinear, a linear relationship was assumed between the inputs and the net benefit for the EVSI calculation. The impact of this assumption is shown in the partial EVPI estimates in Figure 11. The difference between the partial EVPI estimates for the non-linear versus linear assumption for the probability of sustaining benefits in subsequent years is negligible across the range of cost-effectiveness thresholds. The difference between the estimates for the 1-year QoL improvement is more pronounced. The estimate under the linear assumption is shifted to the right of the non-linear EVPPI, peaking at a threshold of £21,000 per QALY as opposed to £18,643 (maximum uncertainty), as in the non-linear case. Under the linear assumption, the partial estimate for the 1-year QoL improvement is approximately 5% more than the non-linear estimate at a threshold of £20,000. The small difference across the range of cost-effectiveness thresholds suggests that the non-linearity of the model has only a limited impact on the results. Therefore, the assumption of linearity in the EVSI calculations seems reasonable (and reduces the computational time substantially).

**FIGURE 11 Expected value of perfect information for parameters: linear assumption versus non-linear estimate.**
Appendix 7

Exercise used to elicit the beliefs of clinical experts

Elicitation exercise details

(Please read before beginning the exercise)

Introduction to the exercise

In the absence of trial data, we would like you to give us your expert opinion on the duration of QoL benefits over time for patients with angina pectoris receiving treatment with EECP.

Please make sure you read the information at the top of each question before attempting to answer it.

Please do not discuss your responses with other individuals. We are interested in your personal beliefs concerning each question.

Background information

The multicentre randomised control trial, MUST-EECP, evaluated QoL in patients receiving active EECP (treatment group) versus inactive EECP (control group). At the end of treatment and at 1-year follow-up, patients who had received active EECP showed greater improvements in QoL than those who had received inactive EECP. The incremental difference in benefits between the active and inactive EECP treatment arms at 1-year follow-up was of a similar magnitude to the incremental difference at the end of treatment. This suggests that QoL benefits from EECP are fully sustained at 1-year follow-up.

In this exercise, we would like you to determine the proportion of patients who will continue to sustain their QoL benefits in subsequent years.

In answering the questions, we would like you to assume that patients have any additional repeat procedures (or top-up sessions) when they require them. Therefore, your answers to all questions are conditional on patients receiving as many top-up sessions as might be appropriate.

Format of answers

In the following questions, information is requested using a grid. Each column represents a range of potential values for a piece of data. We request that you place 20 crosses in each grid. We would like you to place all 20 crosses in one or more columns to represent your current belief and uncertainty about that particular question. For example, if you are completely certain about the answer, then place all 20 crosses in one column of the grid.

Please begin by placing two of the crosses at the upper and lower limits of your belief about the piece of data. You should then place the remaining 18 crosses so as to express your remaining uncertainty about the particular piece of data (see example shown below in Figure 12). Use the letter X on your keyboard to represent the crosses. It is important that you place all 20 crosses in the grid.
YOU ARE NOW READY TO START THE EXERCISE

FIGURE 12 Example grid.
**QUESTION 1 – Sustained duration of QoL benefits at year 2 following treatment with EECP**

We would like you to determine the proportion of patients in year 2 who are likely to sustain the average QoL benefits seen at year 1 following end of treatment.

Question 1: In year 2, what proportion of patients would you expect to sustain the year 1 QoL benefits?

Please place 20 crosses in the grid

![Proportion of patients sustaining QoL benefits in year 2 (%)](image)

Question 1b: Given your response above, do you expect the proportions to be different in subsequent years?

- **YES**  
  Please continue to Question 2 on the next page.

- **NO**  
  You have now completed the questionnaire. Many thanks for your responses. Please feel free to give us any additional feedback.
QUESTION 2 – Sustained duration of QoL benefits at year 3 following treatment with EECP

Given that patients have sustained benefits at year 2, we would like you to determine the proportion of patients in year 3 who are likely to sustain the average QoL benefits seen at year 1 following end of treatment.

Question 2: In year 3, what proportion of sustained year 2 patients would you expect to sustain the year 1 QoL benefits?

Please place 20 crosses in the grid

Question 2b: Given your response above, do you expect the proportions to be different in subsequent years?

YES  You have now completed the questionnaire. Many thanks for your responses. Please feel free to give us any additional feedback.

NO   Please continue to Question 3 on the next page.
Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Mela J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Porshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brehner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.

No. 4
A cost-utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamara P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, et al.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.
No. 15 Ethical issues in the design and conduct of randomised controlled trials.
   A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16 Qualitative research methods in health technology assessment: a review of the literature.
   By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17 The costs and benefits of paramedic skills in pre-hospital trauma care.
   By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18 Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

No. 19 Systematic reviews of trials and other studies.
   By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20 Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prosthesis.

Volume 3, 1999

No. 1 Informed decision making: an annotated bibliography and systematic review.

No. 2 Handling uncertainty when performing economic evaluation of healthcare interventions.
   A review by Briggs AH, Gray AM.

No. 3 The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

No. 4 A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.

No. 5 Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
   By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PG.

No. 6 Assessing the costs of healthcare technologies in clinical trials.
   A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7 Cooperatives and their primary care emergency centres: organisation and impact.
   By Hallam L, Henthorne K.

No. 8 Screening for cystic fibrosis.
   A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9 A review of the use of health status measures in economic evaluation.
   By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10 Methods for the analysis of quality-of-life and survival data in health technology assessment.
   A review by Billingham LJ, Abrams KR, Jones DR.

No. 11 Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
   By Zeuner D, Aes C, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12 Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

No. 13 'Early warning systems' for identifying new healthcare technologies.
   By Robert G, Stevens A, Gabbay J.

No. 14 A systematic review of the role of human papillomavirus testing within a cervical screening programme.

No. 15 Near patient testing in diabetes clinics: appraising the costs and outcomes.
   By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16 Positron emission tomography: establishing priorities for health technology assessment.
   A review by Robert G, Milne R.

No. 17 (Pt 1) The debridement of chronic wounds: a systematic review.
   By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2) Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
   By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18 A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.

No. 19 What role for statins? A review and economic model.

No. 20 Factors that limit the quality, number and progress of randomised controlled trials.
   A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kintana S, et al.

No. 21 Antimicrobial prophylaxis in total hip replacement: a systematic review.
   By Glenny AM, Song F.

No. 22 Health promoting schools and health promotion in schools: two systematic reviews.
   By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23 Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greening P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sovden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spilby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Dudley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O’Meara S, Wilson P, Golder S, Kleinjnen J.

No. 16

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleinjnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients’ outcome influenced by GPs’ referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic review of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O’Meara S, Callum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burl's A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Dalky, et al.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O’Meara S, Renfrew MJ, Woolridge M, Sovden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Briafas P, Jordan R, Fry-Smith A, Burl's A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glucocorticoid IIb/IIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleinjnen J, ter Riet G.
No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Loug G, Towler Ton.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By Macleod MR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HJS, Blaxill JM, Evans JA, et al.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer’s disease: a rapid and systematic review.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Rensma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, et al.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Johanputra P, Parry D, Fry-Smith A, Burd A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O’Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O’Meara S, Rensma R, Sharran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Hillcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.

No. 22
The measurement and monitoring of surgical adverse events.
- By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
- By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
- By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
- By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
- By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
- By Brooks ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
- By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.

No. 36
Cost analysis of child health surveillance.
- By Sanderson D, Wright D, Acton C, Durec D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
- By Hearshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin’s lymphoma: a systematic review and economic evaluation.

No. 4
A systematic review of discharge arrangements for older people.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
- By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
- By O’Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.

No. 8
Promoting physical activity in South Asian Muslim women through ‘exercise on prescription’.
- By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
- By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
- By Scott DA, Loveman E, McIntyre I, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzell M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FY, et al.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burl A.

No. 18

No. 19
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, et al.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burl A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenhauser E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculptor M, Mather L, Reimsmra R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIB/IIIa antagonists.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.

No. 28
Clinical effectiveness and cost—consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost-utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Juni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn’s disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burl A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing’s sarcoma and neuroblastoma.

No. 6
The cost-effectiveness of screening for Helicobacter pylori to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women’s preferences in the management of menorrhagia.

No. 9
Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.

No. 11
First and second trimester antenatal screening for Down’s syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, et al.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GJ, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21

No. 22
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chikot J, Brennan A, Booth A, Karron J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allison S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchins HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capectabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthalet E, Cowan J, Brewer N.

No. 33
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
No. 35  Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.

No. 36  A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
   By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37  Redesigning postnatal care: a randomised controlled trial of protocol-based midwife-led care focused on individual women's physical and psychological health needs.

No. 38  Estimating implied rates of discount in healthcare decision-making.
   By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

   By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, et al.

No. 40  Treatments for spasticity and pain in multiple sclerosis: a systematic review.
   By Beard S, Hunn A, Wight J.

No. 41  The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
   By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42  The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.

Volume 8, 2004

No. 1  What is the best imaging strategy for acute stroke?
   By Warlow JM, Keir SL, Seymour J, Lewis S, Sandrock PG, Dennis MS, et al.

No. 2  Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
   By Mant J, McManus RJ, Oakes RAI, Delaney BC, Barton PM, Deeks JJ, et al.

No. 3  The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.

No. 4  A systematic review of the role of bisphosphonates in metastatic disease.

No. 5  Systematic review of the clinical effectiveness and cost-effectiveness of capetitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
   By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riensma R.

No. 6  Effectiveness and efficiency of guideline dissemination and implementation strategies.

No. 7  Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
   By Bryant J, Clegg AJ, Siddhu MK, Brodin H, Royle P, Davidson P.

No. 8  Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
   By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9  Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
   By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10  A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.

No. 11  The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.

   By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

   By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Pyllaki MA, Cowan J.

No. 14  Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.

No. 15  Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.

No. 16  A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.

No. 17  Does early magnetic resonance imaging improve influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
   By Gilbert FJ, Grant AM, Gillan MG, Vale L, Scott NW, Campbell MK, et al.

No. 18  The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
   By Clark W, Jovanputra P, Barton P, Burds A.
No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.

No. 20
Liquor-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.

No. 27
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
By Dalziel R, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin’s lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, et al.

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, et al.

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebisch I, Taylor FC, Burke M, West RR, et al.

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine.
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.
No. 46  Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.

No. 47  Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48  Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.

No. 49  Generalisability in economic evaluation studies in healthcare: a review and case studies.

No. 50  Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.

Volume 9, 2005

No. 1  Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.

No. 2  Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3  Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.

No. 4  Randomised evaluation of alternative electrourgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5  A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenefelt J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6  Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7  Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, et al.

No. 8  Lay public’s understanding of equipoise and randomisation in randomised controlled trials.

No. 9  Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10  Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.

No. 11  Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.

No. 12  A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13  Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearson P, Bryan S, Hyde C.


No. 15  Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.

No. 16  A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.

No. 17  Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.

No. 18  A randomised controlled comparison of alternative strategies in stroke care.
By Kafra L, Evans A, Perez I, Knupp M, Swift C, Donaldson N.

No. 19  The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20  Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21  Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.

No. 22  A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.
No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.

No. 26
Indirect comparisons of competing interventions.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants’ and professionals’ preferences in randomised controlled trials.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty or total hip arthroplasty.
By Heating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer’s disease.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranwick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.

No. 7

No. 8
Surveillance of Barrett’s oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, et al.

No. 15

No. 16

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, et al.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.

No. 19
Cognitive behavioural therapy in addition to antispasmodic medication for irritable bowel syndrome in primary care: randomised controlled trial.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry’s disease and mucopolysaccharidosis type I.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.


No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher’s disease: a systematic review.


No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.


No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.


No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost-utility for these groups in a UK context.


No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.

By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29

By Harvey S, Stevens K, Harrison D, Armstrong SJ, et al.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.

By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.


No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.


No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.


No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.


No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.


No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.


No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.

By O’Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38


No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.

By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hills G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).


No. 41
The clinical and cost-effectiveness of oxaliplatin and capcitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.

By Pandsor A, Egginton S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.


No. 43
Telemedicine in dermatology: a randomised controlled trial.

By Bowns JR, Collins K, Walters SJ, McDonagh AJG.

No. 44


No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.


No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.


No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.


No. 48
Evaluation of the ventricular assist device programme in the UK.

By Yao G, Albon E, Ady I, Milford D, Bayliss S, Ready A, et al.

No. 50  Amniocentesis results: investigation of anxiety. The ARIA trial.

Volume 11, 2007

No. 1  Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.

No. 2  A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.

No. 3  A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.

No. 4  The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5  A systematic review of qualitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.

No. 6  Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.

No. 7  Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8  Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.

No. 9  Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.

No. 10  Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.

No. 11  Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12  Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13  A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.

No. 14  A systematic review and economic evaluation of statins for the prevention of coronary events.

No. 15  A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.

No. 16  Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17  Screening for type 2 diabetes: literature review and economic modelling.

No. 18  The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.

No. 19  The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20  A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.

No. 21  The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22  A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.

No. 23  Systematic review of the effectiveness of preventing and treating Staphylococcus aureus carriage in reducing peritoneal catheter-related infections.
No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O’Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummings E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carbustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowden C, Francis D, Elbourne D, McDonald AM, Knight R, et al.
No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leonitiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, et al.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hamney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.

No. 2
‘Cut down to quit’ with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.

No. 4
By Charlesworth G, Shepstone L, Wilson E, Thalanyi M, Mugford M, Boland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.

No. 13
Stepped treatment of older adults on laxatives. The STOOLL trial.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta, agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.

No. 28
Intravenous magnesium sulphate and salbutamol for prevention of arrhythmic fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.

No. 31
The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.

No. 36
Immunophrophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandrock J, Burris A.

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosterosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawlin A, Papaioannou D.

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
No. 10  
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.  
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11  
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.  

No. 12  
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.  
By Hobart J, Cano S.

No. 13  
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.  
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, et al., on behalf of the CAST trial group.

No. 14  
Non-occupational postexposure prophylaxis for HIV: a systematic review.  
By Bryant J, Baxter L, Hird S.

No. 15  
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.  

No. 16  
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.  

No. 17  
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.  
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18  
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.  

No. 19  
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.  

No. 20  
Systematic review of respite care in the frail elderly.  

No. 21  
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).  

No. 22  
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.  

No. 23  
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.  
Health Technology Assessment programme

Director,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Deputy Director,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Deputy Chair,
Professor Jon Nicholl,
Director, Medical Care Research Unit, University of Sheffield

Dr Bob Coates,
Consultant Advisor, NETSCC, HTA

Dr Andrew Cook,
Consultant Advisor, NETSCC, HTA

Dr Peter Davidson,
Director of Science Support, NETSCC, HTA

Professor Robin E Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Dr Nick Hicks,
Director of NHS Support, NETSCC, HTA

Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), Department of Health, London

Ms Lynn Kerridge,
Chief Executive Officer, NETSCC and NETSCC, HTA

Dr Ruairidh Milne,
Director of Strategy and Development, NETSCC

Dr Andrew Farmer,
Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Deborah Ashby,
Professor of Medical Statistics, Queen Mary, University of London

Professor John Cairns,
Professor of Health Economics, London School of Hygiene and Tropical Medicine

Professor Peter Croft,
Director of Primary Care Sciences Research Centre, Keele University

Professor Nicky Cullum,
Professor of Centre for Evidence-Based Nursing, University of York

Professor Jenny Donovan,
Professor of Social Medicine, University of Bristol

Professor Steve Halligan,
Professor of Gastrointestinal Radiology, University College Hospital, London

Professor Freddie Handys,
Professor of Urology, University of Sheffield

Professor Allan House,
Professor of Liaison Psychiatry, University of Leeds

Dr Martin J Landray,
Reader in Epidemiology, Honorary Consultant Physician, Clinical Trial Service Unit, University of Oxford

Professor Stuart Logan,
Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter and Plymouth

Dr Rafael Perera,
Lecturer in Medical Statistics, Department of Primary Health Care, University of Oxford

Professor Ian Roberts,
Professor of Epidemiology & Public Health, London School of Hygiene and Tropical Medicine

Professor Mark Sculpher,
Professor of Health Economics, University of York

Professor Helen Smith,
Professor of Primary Care, University of Brighton

Professor Kate Thomas,
Professor of Complementary & Alternative Medicine Research, University of Leeds

Professor David John Torgerson,
Director of York Trials Unit, University of York

Professor Hywel Williams,
Professor of Dermato-Epidemiology, University of Nottingham

Observers

Ms Kay Pattison,
Section Head, NHS R&D Programmes, Research and Development Directorate, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

© 2009 Queen’s Printer and Controller of HMSO. All rights reserved.
Diagnostic Technologies & Screening Panel

Members

Chair, 
Professor Paul Glaziov,
Professor of Evidence-Based Medicine, University of Oxford

Deputy Chair,
Dr David Elliman,
Consultant Paediatrician and Honorary Senior Lecturer, Great Ormond Street Hospital, London

Members

Dr Stephanie Dancer, 
Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Ewlyn, 
Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, 
Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, 
Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, 
Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, 
Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, 
Programme Manager, UK National Screening Committee

Dr Michael Millar, 
Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, 
Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, 
Service User Representative

Dr David Elliman,
Deputy Chair,
Health Technology Assessment programme

Observers

Dr Tim Elliott,
Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody,
Programme Manager, Neuroscience and Mental Health Board

Dr Ursula Wells, 
Principal Research Officer, Department of Health

Dr W Stuart A Smellie, 
Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, 
Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, 
Service User Representative

Dr Graham Taylor,
Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

Pharmaceuticals Panel

Members

Chair, 
Professor Robin Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Deputy Chair, 
Professor Imti Choonaar,
Professor in Child Health, University of Nottingham

Members

Dr Peter Elton, 
Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre, 
Research Fellow, Division of Psychological Medicine and Psychiatry, King’s College London

Mrs Barbara Greggains, 
Service User Representative

Dr Bill Gutteridge, 
Medical Adviser, London Strategic Health Authority

Dr Dyfrig Hughes, 
Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, INSMaR, Bangor University

Professor Jonathan Ledermann, 
Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, 
Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, 
Consultant Psychiatrist and Head of Department, University of Birmingham

Dr Andrew Prentice, 
Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

Dr Martin Shelly, 
General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester

Dr Gillian Shepherd, 
Director, Health and Clinical Excellence, Merck Serono Ltd

Mrs Katrina Simister, 
Assistant Director New Medicines, National Prescribing Centre, Liverpool

Mr David Symes, 
Service User Representative

Dr Lesley Wise, 
Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

Observers

Ms Kay Pattison, 
Section Head, NHS R&D Programme, Department of Health

Mr Simon Reeve, 
Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

Dr Heike Weber, 
Programme Manager, Medical Research Council

Dr Ursula Wells, 
Principal Research Officer, Department of Health

Current and past membership details of all HTA programme ‘committees’ are available from the HTA website (www.hta.ac.uk)
# Therapeutic Procedures Panel

### Members

<table>
<thead>
<tr>
<th>Chair</th>
<th>Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deputy Chair</td>
<td>Professor Scott Weich, Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry</td>
</tr>
<tr>
<td></td>
<td>Professor Jane Barlow, Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry</td>
</tr>
<tr>
<td></td>
<td>Ms Maree Barnett, Acting Branch Head of Vascular Programme, Department of Health</td>
</tr>
<tr>
<td>Mrs Val Carlill, Service User Representative</td>
<td>Mrs Anthea De Barton-Watson, Service User Representative</td>
</tr>
<tr>
<td>Mr Mark Emberton, Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London</td>
<td>Professor Steve Goodacre, Professor of Emergency Medicine, University of Sheffield</td>
</tr>
<tr>
<td>Professor Christopher Griffiths, Professor of Primary Care, Barts and The London School of Medicine and Dentistry</td>
<td>Mr Paul Hilton, Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne</td>
</tr>
<tr>
<td></td>
<td>Professor Nicholas James, Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital</td>
</tr>
<tr>
<td></td>
<td>Dr Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge</td>
</tr>
<tr>
<td></td>
<td>Dr Kate Radford, Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston</td>
</tr>
<tr>
<td></td>
<td>Mr Jim Reece, Service User Representative</td>
</tr>
<tr>
<td></td>
<td>Dr Karen Roberts, Nurse Consultant, Dunston Hill Hospital Cottages</td>
</tr>
</tbody>
</table>

### Observers

| Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health | Dr Morven Roberts, Clinical Trials Manager, Medical Research Council |
| Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health | Professor Tom Valley, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool |
| | Dr Ursula Wells, Principal Research Officer, Department of Health |

# Disease Prevention Panel

### Members

<table>
<thead>
<tr>
<th>Chair</th>
<th>Dr Edmund Jessop, Medical Adviser, National Specialist, National Commissioning Group (NCG), London</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deputy Chair</td>
<td>Dr David Pencheon, Director, NHS Sustainable Development Unit, Cambridge</td>
</tr>
<tr>
<td></td>
<td>Dr Elizabeth Fellow-Smith, Medical Director, West London Mental Health Trust, Middlesex</td>
</tr>
<tr>
<td></td>
<td>Dr John Jackson, General Practitioner, Parkway Medical Centre, Newcastle upon Tyne</td>
</tr>
<tr>
<td></td>
<td>Professor Mike Kelly, Director, Centre for Public Health Excellence, NICE, London</td>
</tr>
<tr>
<td></td>
<td>Dr Chris McCall, General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset</td>
</tr>
<tr>
<td></td>
<td>Ms Jeannet Martin, Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust</td>
</tr>
<tr>
<td></td>
<td>Dr Julie Mytton, Locum Consultant in Public Health Medicine, Bristol Primary Care Trust</td>
</tr>
<tr>
<td></td>
<td>Miss Nicky Mullany, Service User Representative</td>
</tr>
<tr>
<td></td>
<td>Dr Julie Mytton, Locum Consultant in Public Health Medicine, Bristol</td>
</tr>
<tr>
<td></td>
<td>Miss Nicky Mullany, Service User Representative</td>
</tr>
<tr>
<td></td>
<td>Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene &amp; Tropical Medicine</td>
</tr>
<tr>
<td></td>
<td>Professor Ken Stein, Senior Clinical Lecturer in Public Health, University of Exeter</td>
</tr>
<tr>
<td></td>
<td>Dr Kieran Sweeney, Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth</td>
</tr>
<tr>
<td></td>
<td>Professor Carol Tannahill, Glasgow Centre for Population Health</td>
</tr>
<tr>
<td></td>
<td>Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick Medical School, Coventry</td>
</tr>
</tbody>
</table>

### Observers

| Ms Christine McGuire, Research & Development, Department of Health | Dr Caroline Stone, Programme Manager, Medical Research Council |
Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford
Professor John Bond, Professor of Social Gerontology & Health Services Research, University of Newcastle upon Tyne
Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham
Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury
Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast
Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London
Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton
Dr Christine Clark, Medical Writer and Consultant Pharmacist, Rosendale
Professor Collette Clifford, Professor of Nursing and Head of Research, The Medical School, University of Birmingham
Professor Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London
Dr Carl Counsell, Clinical Senior Lecturer in Neurology, University of Aberdeen
Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds
Dr Katherine Barton, Information Unit, MIND – The Mental Health Charity, London
Professor Carol Deazeteux, Professor of Paediatric Epidemiology, Institute of Child Health, London
Mr John Dunning, Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge
Mr Jonathan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester
Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne
Professor Pam Enderby, Dean of Faculty of Medicine, Institute of General Practice and Primary Care, University of Sheffield
Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts and The London School of Medicine and Dentistry
Mr Leonard R Fenwick, Chief Executive, Freeman Hospital, Newcastle upon Tyne
Mrs Gillian Fletcher, Antenatal Teacher and Tutor and President, National Childbirth Trust, Henfield
Professor Jayne Franklyn, Professor of Medicine, University of Birmingham
Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London
Professor Fiona Gilbert, Consultant Radiologist and NCRN Member, University of Aberdeen
Professor Paul Gregg, Professor of Orthopaedic Surgical Science, South Tees Hospital NHS Trust
Bec Hanley, Co-director, TwoCan Associates, West Sussex
Dr Maryann L Hardy, Senior Lecturer, University of Bradford
Mrs Sharon Hart, Healthcare Management Consultant, Reading
Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester
Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham
Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London
Professor Allen Hutchinson, Director of Public Health and Deputy Dean of SchARR, University of Sheffield
Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge
Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey
Dr Duncan Kesley, General Practitioner (Dr Butch & Pinny), The Health Centre, Thame
Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London
Mr George Levy, Chief Executive, Motor Neurone Disease Association, Northampton
Professor James Lindsay, Professor of Psychiatry for the Elderly, University of Leicester
Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa
Professor Aliastaire McGuire, Professor of Health Economics, London School of Economics
Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York
Professor Alexander Markham, Director, Molecular Medicine Unit, St James’s University Hospital, Leeds
Dr Peter Moore, Freelance Science Writer, Ashfold
Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust
Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton
Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia
Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool
Mrs Julietta Patrick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield
Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton
Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges
Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton
Professor Peter Sanderson, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh
Dr Susan Schonfeld, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex
Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James’s University Hospital, Leeds
Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth
Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry
Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry
Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council
Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women’s and Children’s Health, Lymington

Current and past membership details of all HTA programme ‘committees’ are available from the HTA website (www.hta.ac.uk)
Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.