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

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

*Corresponding author

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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 due to adverse events 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]. The three non-randomised studies compared EECP with elective percutaneous coronary intervention (PCI) and usual care. There was a high risk of selection bias in all three studies and the results should 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 Prospective Evaluation of EECP in Congestive Heart Failure (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), but the proportion with an improvement in peak VO_2 was similar in both groups. 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 (RR 2.25, 95% CI 1.25–4.06) at 6 months, as was mean exercise duration, MD 34.6 (95% CI –4.86 to 74.06). There were more withdrawals in the EECP 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

Glossary and list of abbreviations

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

ACE	angiotensin converting enzyme
AE	adverse event
CABG	coronary artery bypass graft
CCS	Canadian Cardiovascular Society
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CVD	cardiovascular disease
ECG	electrocardiogram
EECP	enhanced external counterpulsation
ENBS	expected net benefit of sampling
EVI	expected value of information
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
EVSI	expected value of sample information
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IEPR	International EECP Patient Registry
ITT	intention-to-treat
LVEF	left ventricular ejection fraction
MACE	major adverse clinical event
MI	myocardial infarction
MUST-EECP	Multicenter Study of Enhanced External Counterpulsation
NICE	National Institute for Health and Clinical Excellence
NTG	nitroglycerin
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PEECH	Prospective Evaluation of EECP in Congestive Heart Failure
QALY	quality-adjusted life-year
QLI	Quality of Life Index
QoL	quality of life
RCT	randomised controlled trial
SCS	spinal cord stimulation
SE	standard error
SF-36	36-item Short Form health survey
SIGN	Scottish Intercollegiate Guidelines Network
TENS	transcutaneous electrical nerve stimulation
VO_2	volume of oxygen uptake

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.

Executive summary

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.

A broad range of studies was considered for inclusion in the review 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 quality of studies was assessed according to a checklist updated from that developed by Drummond and Jefferson (1996).

A decision model was developed to evaluate a strategy of EECP treatment compared with no treatment in adults with chronic stable angina. This was used to estimate the cost-effectiveness of EECP, in terms of cost per quality-adjusted life-year, under a range of assumptions. Decision uncertainty associated with this analysis was presented and used to inform future research priorities using value of information analysis.

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.

Chapter 1
Background

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.[1] 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.[2,3]

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.[4] Estimates for 65- to 74-year-olds are 6–16% of men and 3–10% of women.[2] 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.[5]

Stable angina is defined as angina symptoms that have followed a predictable pattern over 2 months.[2] 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.[6]

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.[7] The techniques currently used are percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[6]

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.[8] 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.[8] The Scottish Intercollegiate Guidelines Network (SIGN) guidelines for management of refractory angina recommend that, initially, rehabilitative, educational and cognitive behavioural methods should be employed.[6] 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.[6,8]

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.

Chapter 2

Assessment of clinical effectiveness

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 (VO_2)] 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 4[15] 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 angina[18–20] and one multicentre RCT of EECP for heart failure[21] (*Table 1*). Both randomised controlled trials (MUST-EECP and PEECH)[17,21] and a further study[19] 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

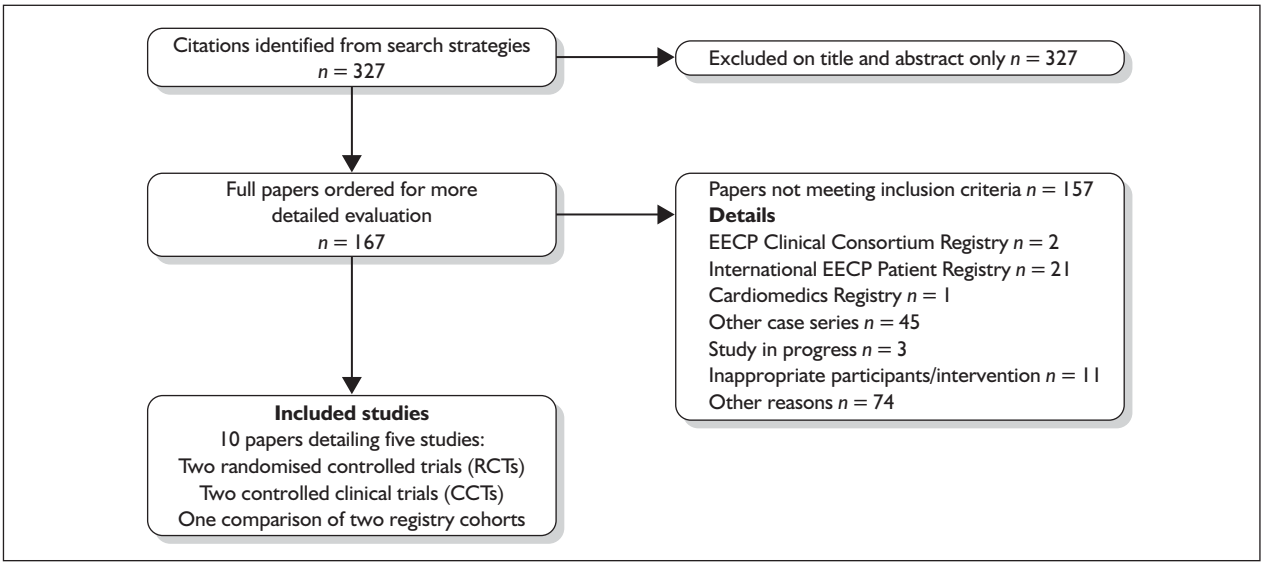

FIGURE 1 *Study selection.*

TABLE 1 *Details of included studies*

	Stable angina				Heart failure
	Randomised controlled trial	Non-randomised controlled studies			Randomised controlled trial
Study design	**Arora *et al.*, 1999[17] MUST-EECP**	**Barsheshet *et al.*, 2008[18]**	**Holubkov *et al.*, 2002[19]**	**Shechter *et al.*, 2003[20]**	**Feldman *et al.*, 2006[21] PEECH**
Comparator	Sham-EECP	Usual care	PCI	Usual care	Usual care
Number of participants	EECP 72	EECP 15	EECP 323	EECP 20	EECP 93
	Control 67	Control 10	Control 448	Control 20	Control 94
Length of follow-up	End of treatment (also 12 months for HRQoL only)	End of treatment	12 months	End of treatment	6 months
Quality assessment[a]					
Randomised	Yes	No	No	No	Yes
Allocation concealment	Yes	No	No	No	Yes
Participant blind	Yes	No	No	No	No
Outcome assessment blind	Yes	No	No	No	Yes
ITT analysis	Partial[b]	No	No	No	Yes

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

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

telephone calls were made to maximise return of the questionnaires. Useable questionnaires were available from 51% of the original study sample.

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 history of previous MI; the intervention group had a considerably longer 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 over-estimate 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*

Outcome	EECP	Control	*p*-value (between groups)	Between group mean difference (MD)/ relative risk (RR) (95% CI)[a]
Numbers randomised	72	67		
Numbers treated	71	66		
Numbers withdrawn	12	1		
Exercise duration (seconds): mean change (SE)	*n* = 57 42 (11)	*n* = 58 26 (12)	*p* > 0.31[b]	MD –16.00 (–47.79 to 15.79)
Time to ≥ 1-mm ST segment depression (seconds): mean change (SE)	*n* = 56 37 (11)	*n* = 56 –4 (12)	*p* = 0.01[a]	MD 41.00 (9.10–73.90)
Angina episodes/day: mean change (SE)	*n* = 71 –0.11 (0.21)	*n* = 66 0.13 (0.22)[c]	*p* < 0.09[d]	MD –0.24 (–0.84 to 0.36)
NTG use/day: mean change (SE)	*n* = 71 –0.32 (0.12)	*n* = 66 –0.10 (0.12)[c]	*p* > 0.1[d]	MD –0.22 (–0.55 to 0.11)
Adverse event	***n* = 71**	***n* = 66**		
Patients with AE, *n*	39	17	*p* < 0.001	RR 2.13 (1.35–3.38)
Withdrawal due to AE, *n*	9	1		
Device-related AE, *n*	37	10	*p* < 0.001	
Non-device-related AE, *n*	33	15	*p* < 0.005	

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[19] 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 known or 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*

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

NS, not significant.
a Calculated from study data available.

differences in baseline characteristics between the two groups, the results for all outcomes need to be treated with considerable caution.

The two studies with a usual care comparator had very small samples, $n = 40$ and $n = 35$, and used patients who refused EECP as the control group.[18,20] In both studies, CCS classification improved with EECP but not with usual care; however, neither study reported a statistical analysis of between group differences. In addition, for CCS classification the data were treated as continuous data, which is inappropriate for this four-category classification.

Summary

Only one RCT of EECP for chronic stable angina was found. This trial focused on improvement in symptoms and exercise duration. Cardiac-related mortality was not reported. In addition, three non-randomised studies with a control group investigated EECP in stable angina populations; because of limitations in the quality of these studies, 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.*,[21] was to assess the benefits of EECP in the treatment of mild to moderate heart failure. Patients were randomised to EECP of 35 1-hour sessions as an adjunct to pharmacotherapy 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 a 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 VO_2. The study was powered (90%) to detect at least a 60-second increase in exercise duration from baseline in 50% of EECP recipients compared with 20% of control subjects, and a 1.25-ml/kg/minute increase in peak VO_2 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 VO_2 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.

TABLE 4 *Results of the PEECH trial*

Outcome	EECP	Control	*p*-value (between groups)	Mean difference (MD)/relative risk (RR) and 95% CI[a]
Exercise duration (percentage with at least a 60-second increase in exercise duration from baseline to 6 months)	35.4%	25.3%	$p = 0.016$[b]	RR 1.39 (0.89–2.16)
Exercise duration [mean change in exercise duration from baseline(s) (SE)]				
1-week follow-up	*n* = 77 26.4 (12.2)	*n* = 78 –5.5 (11.7)	$p = 0.010$[b]	MD 31.9 (–1.23 to 65.03)
3-month follow up	*n* = 78 34.5 (13.9)	*n* = 82 –7.0 (12.7)	$p = 0.014$[b]	MD 41.5 (4.72–78.28)
6-month follow up	*n* = 79 24.7 (15.2)	*n* = 83 –9.9 (13.2)	$p = 0.013$[b]	MD 34.6 (–4.86 to 74.06)
NYHA classification (percentage with improvement in classification)[c]	***n* = 93**	***n* = 94**		
1-week follow-up	33.3%	11.4%	$p < 0.001$[b]	RR 2.85 (1.52–5.32)
3-month follow-up	31.6%	12.2%	$p < 0.02$[b]	RR 2.66 (1.42–5.01)
6-month follow-up	31.3%	14.3%	$p < 0.01$[b]	RR 2.25 (1.25–4.06)
Peak VO_2 (percentage with at least a peak VO_2 increase of at least 1.25 ml/kg/minute from baseline to 6 months)	22.8%	24.1%	$p = 0.698$[b]	RR 0.96 (0.57–1.63)
VO_2 related [mean change in peak VO_2 (ml/kg/minute) (SE)]				
1-week follow-up	*n* = 77 0.1 (0.3)	*n* = 78 –0.4 (0.3)	$p = 0.071$[b]	MD 0.5 (–0.32 to 1.32)
3-month follow-up	*n* = 78 0.2 (0.3)	*n* = 82 –0.4 (0.3)	$p = 0.119$[b]	MD 0.60 (–0.22 to1.42)
6-month follow-up	*n* = 79 –0.3 (0.3)	*n* = 83 –0.6 (0.3)	$p = 0.315$[b]	MD 0.30 (–0.53 to 1.13)
QoL [mean change in QoL score (CIs) using Minnesota Living with Heart Failure Questionnaire][d]				
1-week follow-up	–8.8 (–7 to –10.9)	–3.5 (–1.5 to –5)	$p = 0.01$[e]	
3-month follow-up	–7.2 (–4.7 to –9.5)	–2.8 (–1 to –4.6)	$p = 0.01$[e]	
6-month follow-up	–3.5 (–1.3 to –6.0)	–2.8 (–0.5 to –4.5)	$p = 0.32$[e]	
Adverse events				
Patients with serious AE, *n* (%)	27 (30.3)	26 (29.5)	NS	RR 1.05 (0.67–1.66)
Withdrawal due to AE, *n* (%)	11 (11.8)	3 (3.2)	NS	
Number of predefined clinical events	89	88	NS	

NS, not stated.
a Calculated from study data available.
b From logistic regression that factored site and baseline.
c Number of patients in analysis unclear, but assumed to be the number of patients reported in each study arm for analytical purposes.
d 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.
e 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 VO_2 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 (CCTR), 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.[23] 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 EECP 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 EECP for the treatment of chronic stable angina were reported, but no citation or reference to the study was given. The manufacturer of EECP, Vasomedical, 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'.[24]

Overview

The study was designed to investigate the potential economic impact of EECP. A cost–utility analysis was performed to determine whether improvement in angina functional grades with EECP, 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) EECP 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 EECP. 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 *et al.*[25] and Kandzari *et al.*[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 *et al.* 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 *et al.* 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.[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 pre-treatment medication usage patterns reported in Michaels *et al.*[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.[28] 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.[29,30] 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.[31]

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.[32] 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.[33] 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.

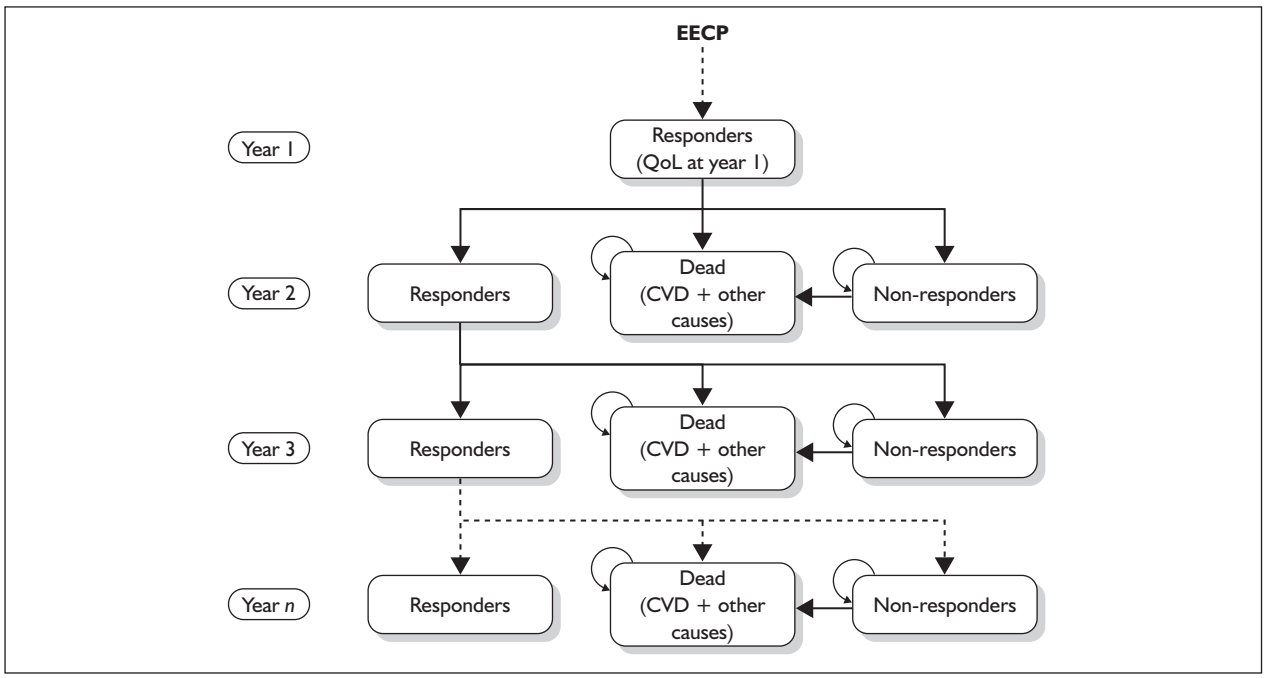

FIGURE 2 *Structure of the model for EECP.*

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.[17] 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.[22] 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.*,[34] 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.[35] 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.[30] *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.[36]

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.[39] These techniques involve asking clinical experts to elicit their beliefs about model parameters with or without some estimate of

TABLE 5 *Utility improvement for EECP relative to no treatment at 1 year*

	Mean change from baseline to 1 year following end of treatment				
Parameter	**Active EECP**	**Inactive EECP**	**Incremental mean change (SE)[a]**	**Distribution**	**Source**
Utility	0.1068	0.0351	0.0717 (0.036)	Beta ($\alpha = 3.64$, $\beta = 47.13$)	Arora *et al.*, 2002[22]

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

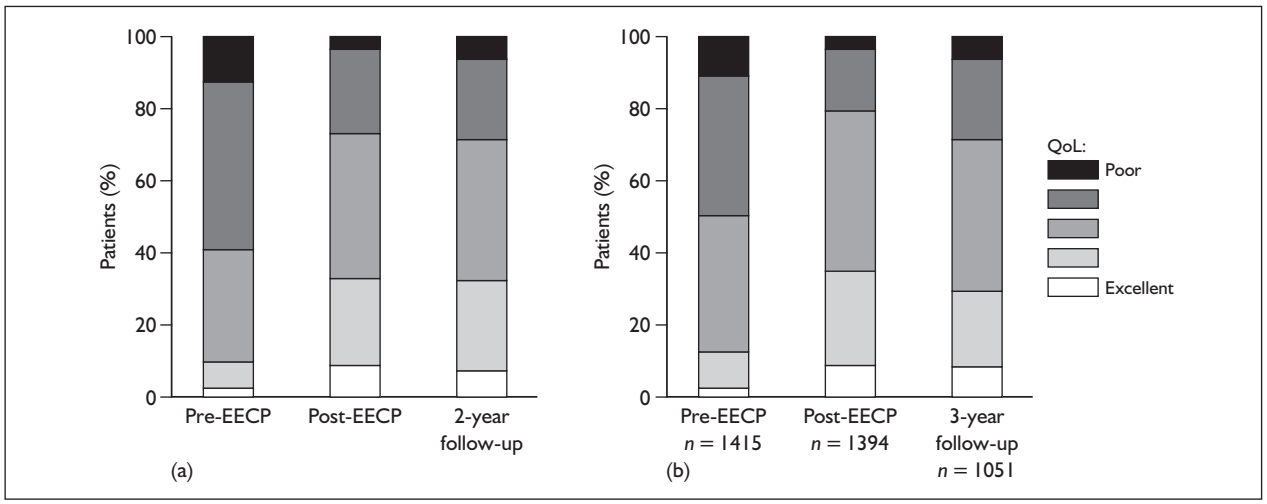

FIGURE 3 Quality of life *(QoL) rated as poor (black bars) to excellent (white bars) in terms of the five-point rating scale at (a) 2-year[37] and (b) 3-year[38] follow-up after EECP treatment.*

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.[40] 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.[41] Each expert was given equal weight, and the pooled result was assumed to be representative of the beliefs of UK clinicians. A

TABLE 6 *Mean and standard deviation (SD) of the elicited values for each expert separately, and linearly pooled results across experts*

	Mean probability of sustaining year 1 QoL benefits in subsequent years[a] (SD)		
	Year 2	**Year 3**	**Year 4+**
Expert 1	0.670 (0.091)	0.600 (0.082)	0.526 (0.088)
Expert 2	0.807 (0.047)	0.886 (0.052)	0.886 (0.052)
Expert 3	0.785 (0.039)	0.700 (0.057)	0.675 (0.075)
Expert 4	0.605 (0.104)	0.605 (0.104)	0.605 (0.104)
Expert 5	0.908 (0.036)	0.905 (0.035)	0.898 (0.043)
Pooled result	0.757 (0.126)	0.742 (0.150)	0.719 (0.168)

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

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

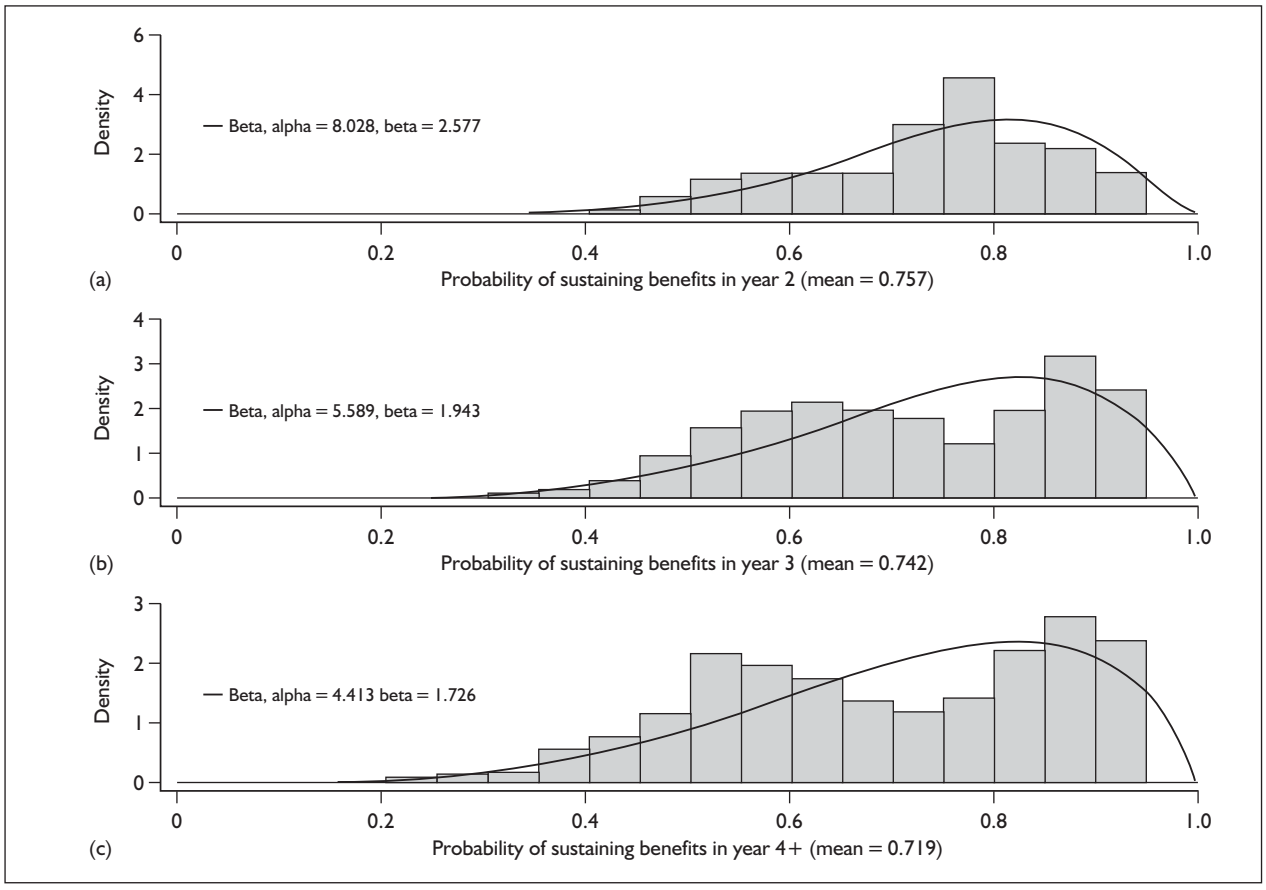

FIGURE 4 *Pooled distribution of elicited responses from five experts for the probability of sustaining QoL benefits in (a) year 2, (b) year 3 and (c) year 4+, with a beta distribution fitted to the data.*

the EUropean trial on Reduction Of cardiac events with Perendopril in stable coronary Artery disease (EUROPA) trial.[42] 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.[42] 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.[43] 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-EECP 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.[44] 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 3 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.[45] 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*

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

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.[46] 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.[22]

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.[47] 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.[28] 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.[48] 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*

Scenario	Element	Position in base-case analysis	Variation in sensitivity analysis
1	Elicited expert values for the probability of sustaining QoL benefits from EECP over time	Linearly pooled values across experts with beta distribution fitted	Empirical values from each expert used in separate analyses Linearly pooled empirical values across experts used with no distribution specified
2	Costs of EECP	Total cost is £4347 per patient	Lower and higher costs assumed (from £1000 lower to £1000 higher)
3	Probability of repeat EECP sessions	Within 2 years of EECP, the rate of repeat procedures is 18%	Within 2 years of EECP, the rate of repeat procedures varied from 10% to 30%
4	Population	92% male, 8% female Average age is 64 years	Separate analysis for men and women Alternative starting ages assumed from 55 to 70 years
5	Discount rate	3.5% applied to both costs and outcomes	6% costs, 1.5% outcomes

TABLE 9 *Base-case estimates of mean lifetime costs and QALYs, together with best- and worst-case scenarios for the duration of QoL benefits*

Base-case analysis using pooled expert elicitation values				Probability of being cost-effective for the cost-effectiveness threshold	
Treatment	**Cost**	**QALY**	**ICER**	**£20,000**	**£30,000**
EECP	£4750	7.492	£18,643	0.444	0.698
No treatment	£0	7.237		0.556	0.302
Worst-case scenario					
EECP	£4464	7.289	£63,072	0.001	0.032
No treatment	£0	7.237		0.999	0.968
Best-case scenario					
EECP	£5117	8.117	£5831	0.966	0.991
No treatment	£0	7.237		0.034	0.009

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]

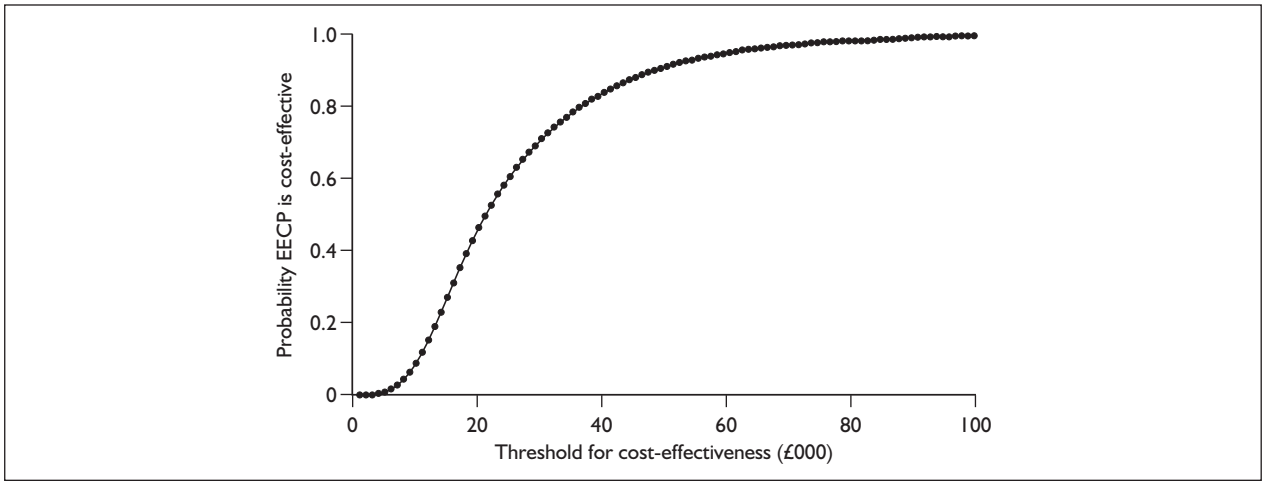

FIGURE 5 *Cost-effectiveness acceptability curve for base-case analysis.*

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. A

TABLE 10 *Summary of sensitivity analysis results*

Scenario	Element	Variation in sensitivity analysis	ICER	Probability EECP is cost-effective for the cost-effectiveness threshold	
				£20,000	£30,000
Base-case	Not applicable	Not applicable	£18,643	0.444	0.698
1	Elicited expert values for the probability of sustaining QoL benefits from EECP over time	Expert 1 empirical values	£28,158	0.194	0.483
		Expert 2 empirical values	£12,235	0.734	0.894
		Expert 3 empirical values	£21,473	0.386	0.666
		Expert 4 empirical values	£27,245	0.213	0.481
		Expert 5 empirical values	£10,664	0.805	0.931
		Pooled expert empirical values	£18,237	0.463	0.701
2	Costs of EECP sessions	Lower and higher costs assumed (from £1000 lower to £1000 higher)			
		–£1000	£14,354	0.618	0.821
		–£500	£16,499	0.529	0.764
		+£500	£20,788	0.372	0.639
		+£1000	£22,932	0.310	0.579
3	Probability of repeat EECP sessions	Within 2 years of EECP, probability varied from 10% to 30%			
		10%	£18,021	0.469	0.718
		15%	£18,424	0.452	0.704
		25%	£19,117	0.428	0.685
		30%	£19,413	0.417	0.676
4	Population	Separate analysis for men and women			
		Men (100%)	£18,666	0.444	0.697
		Women (100%)	£17,996	0.464	0.711
		Alternative starting ages assumed from 55 to 70 years			
		55 years	£17,567	0.476	0.721
		60 years	£17,951	0.466	0.714
		70 years	£19,658	0.416	0.680
5	Discount rate	6% costs, 1.5% outcomes	£17,381	0.484	0.726

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.[32] It also provides an indication of where additional research is most valuable.[50] 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.[51] 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 θ, the EVPI is the difference between the expected value of the decision made on the basis of existing information ($\max_j[E_\theta\{NB(j, \theta)\}]$), and the value of the decision made with perfect information ($\max_j\{NB(j, \theta)\}$), averaged over all possible realisations of uncertainty ($E_\theta[\max_j\{NB(j, \theta)\}]$):

$$EVPI = E_\theta[\max_j\{NB(j, \theta)\}] - \max_j[E_\theta\{NB(j, \theta)\}]$$

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:

$$EVPI * \left(P_0 + \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} \right)$$

where P_0 is the prevalent population, 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.

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.[52] 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.[52] 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

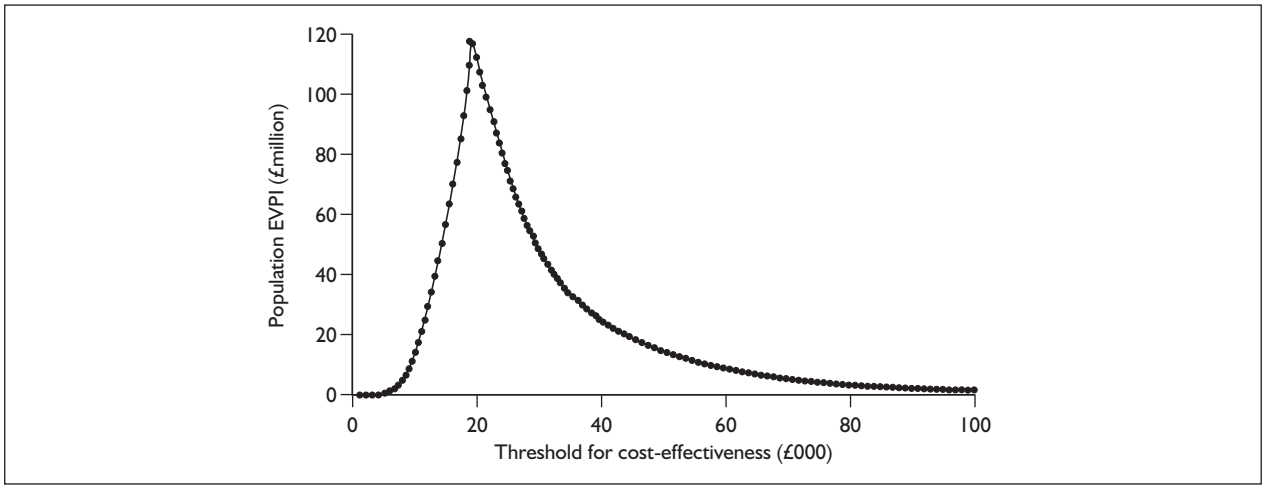

FIGURE 6 *EVPI for base-case model.*

TABLE 11 *Individual patient and population EVPI for selected values of the threshold for the base-case model*

	Individual patient EVPI for the cost-effectiveness threshold		Population EVPI for the cost-effectiveness threshold	
Scenario	**£20,000**	**£30,000**	**£20,000**	**£30,000**
Base-case	£971.29	£440.16	£107,556,668	£48,741,220

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) φ, is the difference between the expected value of the decision made on the basis of existing information ($\max_j[E_\theta\{NB(j, \theta)\}]$), (as with the calculation of decision EVPI) and the value of the decision made with perfect information about φ ($\max_j[E_{\theta|\varphi}\{NB(j, \theta)\}]$). Where perfect information about the parameter φ has no impact on the decision, the information has no value. The value of the decision made with perfect information about φ is averaged over all possible realisations of uncertainty ($E_\varphi[\max_j(E_{\theta|\varphi}\{NB(j, \theta)\})]$) to reflect the fact that the parameter can resolve at any point within the distributions:

$$EVPPI_\varphi = E_\varphi[\max_j(E_{\theta|\varphi}\{NB(j, \theta)\})] - \max_j[E_\theta\{NB(j, \theta)\}]$$

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

Table 12 provides the EVPPI estimates for the three groups of uncertain parameters in the base-case model for selected values of the threshold. The EVPI associated with the 1-year QoL gains from EECP is extremely high and appears to account for the majority of uncertainty in the model. The

TABLE 12 *Individual patient and population EVPPI estimates for selected values of the threshold for the base-case model*

		Individual patient EVPPI for the cost-effectiveness threshold		Population EVPPI for the cost-effectiveness threshold	
Scenario	**Parameters**	**£20,000**	**£30,000**	**£20,000**	**£30,000**
Base-case	All parameters	£971.29	£440.16	£107,556,668	£48,741,220
1	1-year QoL improvement	£784.68	£340.35	£86,892,420	£37,689,025
2	Probability of sustaining QoL benefits in subsequent years	£379.80	£10.14	£42,056,850	£1,122,826
3	Repeat top-up procedures	£0.00	£0.00	£0.00	£0.00

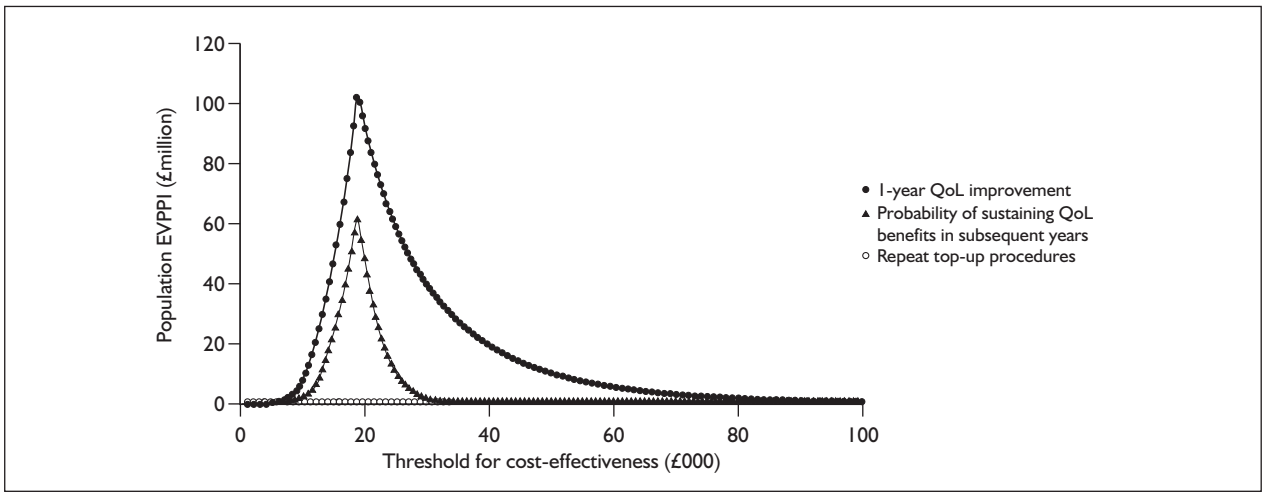

FIGURE 7 *EVPI for parameters in the base-case model.*

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;[33] 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.[46,53,54] 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.[33]

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.[53] 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 θ 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 θ ($E_D[\max_j[E_{\theta|D}\{NB(j, \theta)\}]]$). The EVSI is then expressed as:

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

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:

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

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:

$$C(n) = FC + RC * n + (P_0 + I_1 - n) * \{NB^*(T = 1) - NB^{ST}(T = 1)\} + (n/2) * \{NB^*(T = 1) - NB^o(T = 1)\}$$

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^o 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.[54] 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,

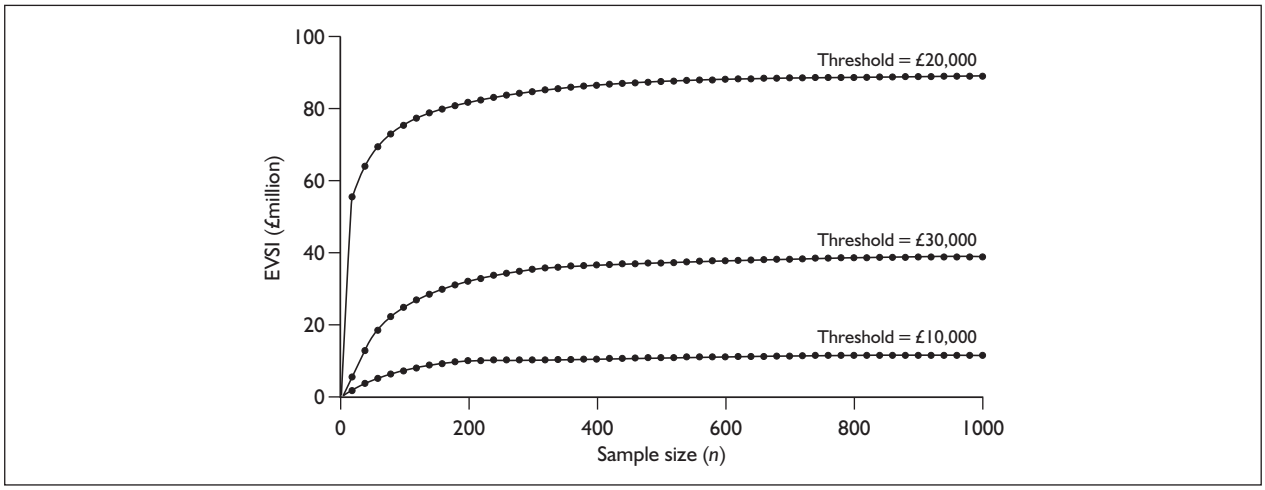

FIGURE 8 *EVSI for the decision problem.*

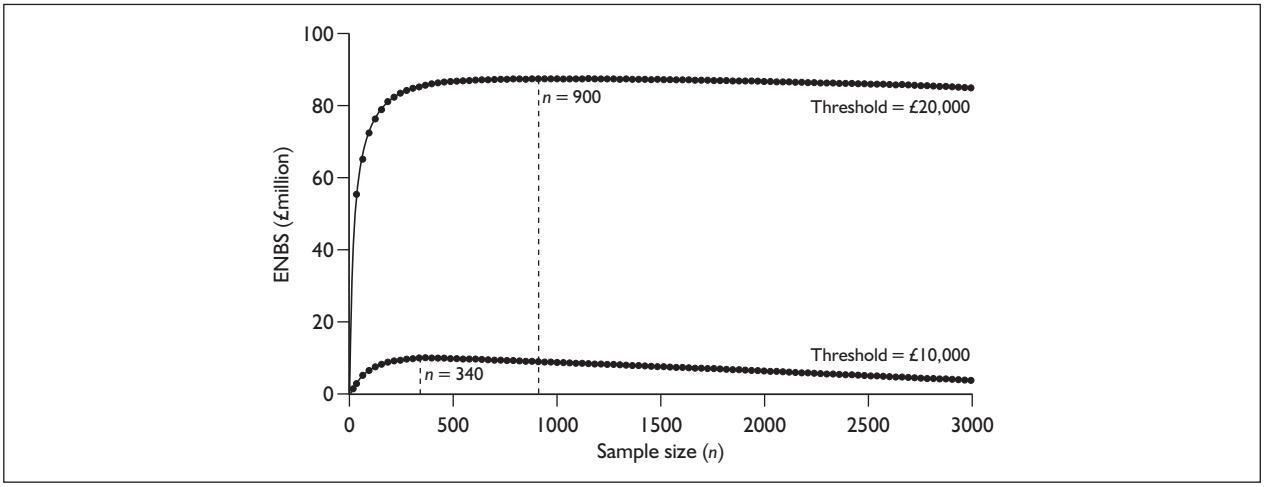

FIGURE 9 *ENBS and optimal sample size.*

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

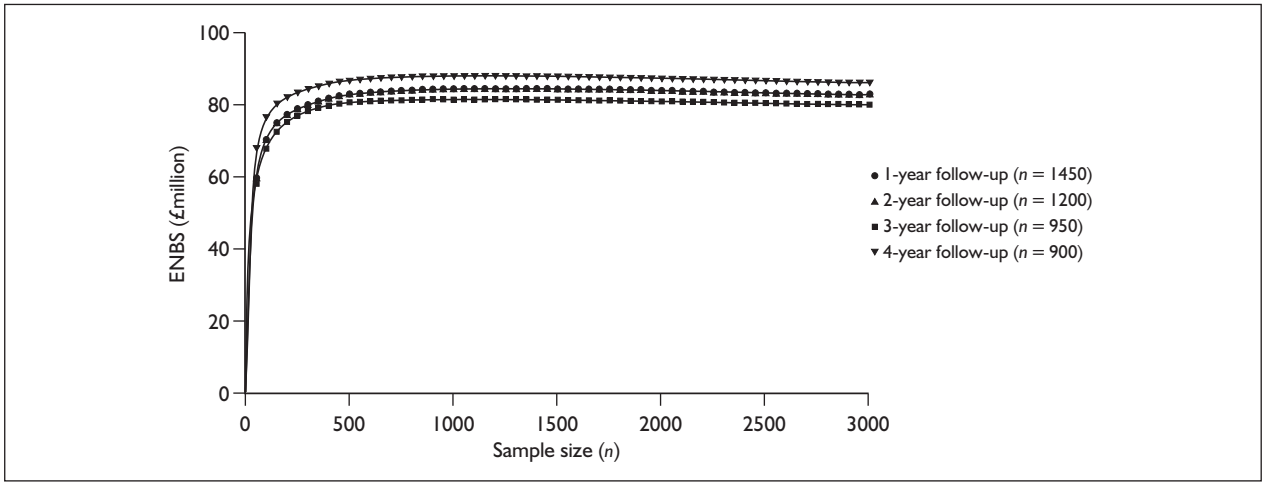

FIGURE 10 *ENBS and optimal sample size for length of follow-up.*

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 RCT[17] (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-2[27] and COURAGE[55]), 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 VO_2 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

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.[58]

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 health-care 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[14] 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.

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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.

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Appendix 1
Searches

Main searches

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

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

EMBASE (Ovid Online – www.ovid.com/)
1980–2007 (week 43)
Searched 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)
Searched 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
Searched on 1 November 2007
Retrieved 1 hit

CENTRAL (The Cochrane Library – www.thecochranelibrary.com/)
Issue 4 2007
Searched 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) (CRD administration database)]
Searched 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/)
Searched on 6 November 2007
Retrieved 0 hits

Search strategy
1. External (w) counterpulsation/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
Searched on 9 November 2007
Retrieved 8 hits

Search strategy
1. external counterpulsation
2. external counter pulsation

3. eecp
4. peech
5. must eecp
6. or/1–5

Clinical Trials.gov (http://clinicaltrials.gov/)
Searched on 09 November 2007
Retrieved 2 hits

Search strategy
The search interface to this resource is a very simple one and the search had to be modified accordingly.

"external counterpulsation" OR "external counter pulsation" OR eecp OR peech

Current Controlled Trials Meta Register (http://controlled-trials.com/mrct/)
Searched on 9 November 2007
Retrieved 6 hits

Search strategy
The search interface to this resource is a very simple one and the search had to be modified accordingly.

"external counterpulsation" OR "external counter pulsation" OR eecp OR peech

Vasomedical website (www.vasomedical.com/)
This site has a browsable section entitled "latest Health Information", which yielded one result.

US Food and Drug Administration (FDA) website (http://www.fda.gov/)
Searched on 13 December 2007
Retrieved 97 hits

Search strategy
The search interface to the FDA website is very simple and the search strategy had to be adapted accordingly.

Two searches were carried out. All of the FDA website was searched.

Search 1
("all of the words") EECP

Search 2
("with the exact phrase") External counterpulsation
("without the words") EECP

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
- EMBASE (Ovid Online – www.ovid.com/) – Week 12 2008 – 3 new records
- 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
- CENTRAL (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
- NHS EED (NHS Economic Evaluation Database) (CRD administration database) –28 March 2008 – no new records

Additional economics searching

MEDLINE (Ovid Online – www.ovid.com/)
1950–January 2008 (week 3)
Searched on 29 January 2008
Retrieved 162 hits

MEDLINE In-process (Ovid Online – www.ovid.com/)
January 28 2008
Searched 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 multi attribute$health).ti,ab.
12. (health utilit$index or health utilit$indices).ti,ab.
13. (multiattribute$theor$or multi attribute$theor$or multiattribute$analys$or multi attribute$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 shortform 6d or sf six$or shortform six$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$health or multi attribute$health).ti,ab.
12. (health utilit$index or health utilit$indices).ti,ab.
13. (multiattribute$theor$or multi attribute$theor$or multiattribute$analys$or multi attribute$analys$).ti,ab.
14. classification of illness state$.ti,ab.
15. health state$utilit$.ti,ab.
16. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
17. (sf 6d or sf6d or short form 6d or shortform 6d or sf six$or shortform 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

CINAHL – Cumulative Index to Nursing & Allied Health Literature (Ovid Online – www.ovid.com/)
1982–December 2007 (week 1)
Searched on 29 January 2008
Retrieved 10 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$or time trade off or time tradeoff or tto or willingness to pay).ti,ab.
5. (disutilities or disutility or daly).ti,ab.
6. disability adjusted life.ti,ab.
7. qwb$.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$health or multi attribute$health).ti,ab.
12. (health utilit$index or health utilit$indices).ti,ab.
13. (multiattribute$theor$or multi attribute$theor$or multiattribute$analys$or multi attribute$analys$).ti,ab.
14. classification of illness state$.ti,ab.
15. health state$utilit$.ti,ab.
16. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
17. (sf 6d or sf6d or short form 6d or shortform 6d or sf six$or shortform 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

	Reason for exclusion						
			Study design[c]				
Study	Inappropriate intervention[a]	Inappropriate participants[b]	EECP clinical consortium	International EECP Patient Registry	Cardiomedics Registry	Other case series	Study in progress (authors contacted)
Akhtar *et al.*, 2006[59]	×					×	
Arora *et al.*, 2001[60]						×	
Arora *et al.*, 2005[61]						×	
Bagger, 2007[62]							×
Bagger *et al.*, 2004[63]						×	
Barsness *et al.*, 2001[64]				×			
Bonetti *et al.*, 2003[65]						×	
Cleland, 2007[66]						×	
Cohn and Lawson, 1994[67]						×	
Cohn *et al.*, 1997[68]						×	
Cowie *et al.*, 1999[11]	×						
Dockery *et al.*, 2004[69]						×	
El-Sakka *et al.*, 2007[70]						×	
El-Sakka *et al.*, 2007[71]						×	
Fitzgerald *et al.*, 2003[72]				×			
Fricchione *et al.*, 1995[73]						×	
Gloth and Oken, 1999[74]						×	
Guo *et al.*, 2005[75]		×					
Hall, 2007[76]						×	
Henrikson and Chandra-Strobos, 2004[77]						×	

Study	Reason for exclusion						
			Study design[c]				
	Inappropriate intervention[a]	Inappropriate participants[b]	EECP clinical consortium	International EECP Patient Registry	Cardiomedics Registry	Other case series	Study in progress (authors contacted)
Kaluski *et al.*, 2006[78]						×	
Kasliwal *et al.*, 1996[79]	×						
Lakshmi *et al.*, 2002[80]				×			
Lawson *et al.*, 2007[81]				×			
Lawson *et al.*, 2004[82]				×			
Lawson *et al.*, 2000[83]			×				
Lawson *et al.*, 1998[84]						×	
Lawson *et al.*, 2005[85]				×			
Lawson *et al.*, 2006[86]				×			
Lawson *et al.*, 2007[87]				×			
Lawson *et al.*, 2000[88]						×	
Lawson *et al.*, 1992[89]						×	
Lawson *et al.*, 1996[90]						×	
Lawson *et al.*, 1996[91]						×	
Lawson *et al.*, 1995[92]						×	
Lawson *et al.*, 2001[93]				×			

Study	Reason for exclusion						
			Study design[c]				
	Inappropriate intervention[a]	Inappropriate participants[b]	EECP clinical consortium	International EECP Patient Registry	Cardiomedics Registry	Other case series	Study in progress (authors contacted)
Lawson *et al.*, 2003[94]				×			
Lawson *et al.*, 2005[95]				×			
Lee *et al.*, 2006[96]						×	
Levenson *et al.*, 2007[97]		×					
Linnemeier *et al.*, 2003[98]				×			
Linnemeier *et al.*, 2003[99]				×			
Loh, 2007[100]							×
Loh *et al.*, 2006[101]						×	
Masuda *et al.*, 2004[102]	×						
Masuda *et al.*, 2001[103]						×	
McCullough *et al.*, 2007[104]				×			
McCullough *et al.*, 2006[105]				×			
Michaels *et al.*, 2002[106]	×						
Michaels *et al.*, 2005[45]				×			
Michaels *et al.*, 2001[107]				×			
Michaels *et al.*, 2004[25]				×			
Michaels *et al.*, 2006[108]				×			

Study	Reason for exclusion						
			Study design[c]				
	Inappropriate intervention[a]	Inappropriate participants[b]	EECP clinical consortium	International EECP Patient Registry	Cardiomedics Registry	Other case series	Study in progress (authors contacted)
Michaels *et al.*, 2005[109]						×	
Michaels *et al.*, 2004[110]						×	
Moore, 2007[111]							×
Nichols *et al.*, 2006[112]						×	
Novo *et al.*, 2006[113]						×	
Ochoa *et al.*, 2006[114]						×	
Olsson, 1999[115]	×						
Pettersson *et al.*, 2006[116]						×	
Rana *et al.*, 2005[117]	×						
Sajja *et al.*, 2007[118]						×	
Soran *et al.*, 2002[119]						×	
Soran *et al.*, 2007[120]						×	
Soran *et al.*, 2002[121]				×			
Soran *et al.*, 2006[37]				×			
Springer *et al.*, 2001[122]						×	
Stys *et al.*, 2002[123]						×	
Stys *et al.*, 2001[124]			×				
Sun, 1991[125]						×	
Tartaglia *et al.*, 2003[126]						×	
Urano *et al.*, 2001[127]						×	
Vijayaraghavan *et al.*, 2005[128]					×		
Walker, 2007[129]						×	

Study	Reason for exclusion						
			Study design[c]				
	Inappropriate intervention[a]	Inappropriate participants[b]	EECP clinical consortium	International EECP Patient Registry	Cardiomedics Registry	Other case series	Study in progress (authors contacted)
Weisfogel *et al.*, 2001[130]						×	
Werner *et al.*, 2003[131]						×	
Yavari and Montazeri, 2007[132]						×	
Yi *et al.*, 1999[133]		×					
Youcheng, 1991[134]						×	
Zheng, 1981[135]						×	
Zheng *et al.*, 1983[136]		×					

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

	Study				
Assessment criteria	**Arora et *al.*, 1999[17]**	**Barsheshet et *al.*, 2008[18]**	**Holubkov et *al.*, 2002[19]**	**Shechter et *al.*, 2003[20]**	**Feldman et *al.*, 2006[21]**
Was the method used to assign participants to treatment groups truly random?	Yes	No	No	No	Yes
If non-randomised, describe how participants were allocated to treatment groups	NA	Patients were referred to the EECP programme. The control group consisted of age- and gender-matched patients who refused EECP	Comparison of two registries	The EECP group was recruited from an EECP program. Age- and gender-matched patients who refused EECP were the control group	NA
Was the treatment allocation concealed?	Yes	No	No	No	Yes
Were the treatment groups similar at baseline?	No The EECP group had longer duration of angina and a higher proportion with previous MI	Yes	No The EECP group had higher prevalence of several risk factors	Yes	Yes
If the above answer was no, was this taken into consideration in the analysis or study design?	No	NA	No The authors state it was not appropriate due to the small number of events and other limitations of the data	NA	NA
Did the analysis include an ITT analysis (i.e. were all participants included in the analysis, in the group to which they were allocated)?	Yes (for some outcomes) A partial ITT analysis – two participants who withdrew prior to first treatment were not included in the analysis	No	No	No	Yes
Were appropriate methods used to account for missing data in the ITT analysis?	Unclear	NA	NA	NA	Yes (Last observation carried forward)

Assessment criteria	Study				
	Arora et *al*., 1999[17]	**Barsheshet et *al*., 2008[18]**	**Holubkov et *al*., 2002[19]**	**Shechter et *al*., 2003[20]**	**Feldman et *al*., 2006[21]**
Was any of the outcome assessment blinded?	Yes Investigators collecting and processing data were blinded; participants were blinded; appointments were scheduled to minimise the chance of participants in the two groups meeting	No	No	No	Yes Staff responsible for baseline and follow-up assessment were blinded
Proportion of participants who did not complete the study.	EECP: 13/72 (18%) Control: 2/67 (3%)	0% (none reported)	Unclear	0% (none reported)	EECP 22/93 (23.7%) Control 13/94 (13.8%)

NA, not applicable.

Appendix 4

Data extraction tables for clinical effectiveness review

TABLE 13 *Arora* et al., *1999.*[17] *Related papers: Arora* et al., *2002*[22] *reports data on QoL, 12 months after treatment; conference proceedings – summary of QoL subgroup study*

Methods	Participants	Withdrawals	Outcomes assessed
RCT *Intervention* EECP 35 1-hour sessions of EECP could be given once or twice a day. Protocol-specified applied was 300 mmHg *Details of any other therapy* All medications (except on-demand NTG) remained unchanged throughout the study *Comparator* 35 hours of inactive (sham) counterpulsation. Treatment sessions lasting 1 hour could be given once or twice a day. Cuff pressure was 75 mmHg in this group *Details of any other therapy* All medications (except on-demand NTG) remained unchanged throughout the study *Inclusion criteria* Between 21 and 81 years old CCS Classification I, II or III Documented evidence of coronary artery disease (criteria specified) Have an exercise treadmill test positive for ischaemia *Exclusion criteria* MI or CABG in the preceding 3 months Cardiac catherisation in the preceding 2 weeks Unstable angina Overt congestive heart failure or a left ventricular ejection fraction less than or equal to 30% Significant valvular heart disease Blood pressure > 180/100mmHg Permanent pacemaker or implantable defibrillator Non-bypassed left main stenosis > 50%	*Number allocated to each group* EECP $n = 72$; control $n = 67$ *Age [mean (SD)]* EECP 64 (9); control 62 (9) *Sex (% male)* EECP $n = 61$ (85.9); control $n = 58$ (87.9) *Race,* n *(%)* White: EECP 55 (77.5); control 49 (74.2%) Black: EECP 3 (4.2); control 2 (3.0) Hispanic: EECP 5 (7.0); control 10 (15.2) Asian: EECP 5 (7.0); control 3 (4.5) Other: EECP 3 (4.2); control 2 (3.0) *Condition being treated* Stable angina ***Baseline clinical characteristics*** *CCS classification,* n *(%)* Class I: EECP 17 (25.8); control 19 (26.8) Class II: EECP 34 (51.5); control 35 (49.3) Class III: EECP 15 (22.7); control 17 (23.9) *Exercise duration(s), mean (SE)* EECP ($n = 57$) 426 (20); control ($n = 58$) 432 (22) *Time to ≥ 1-mm ST segment depression, mean seconds (SE)* EECP ($n = 56$) 337 (18); control ($n = 56$) 326 (21) *Angina episodes – angina count (all participants), mean (SE)* EECP 0.76 (0.15); control 0.76 (0.13) *Medication use,* n *(%)* Nitrates: EECP 56 (78.9); control 54 (81.8) Aspirin taken as an antithrombotic: EECP 32 (87.3); control 60 (90.9)	*Number of withdrawals and losses to follow-up: EECP ($n = 13$)* Prior to first treatment $n = 1$ Owing to adverse event $n = 9$ Owing to other medical event $n = 2$ Owing to personal reasons $n = 1$ ETT data were available for 57 of 59 who completed the trial (four protocol violations, seven adverse event withdrawals and three for personal reasons). Some of these withdrawals may already be reported above, as data in the study flow chart and text did not tally *Control* (n = 2) Prior to first treatment $n = 1$ Due to adverse event $n = 1$ ETT duration data were available for 58 of 65 who completed the trial (seven protocol violations and one adverse event withdrawal, which may be the withdrawal already reported) *Did study report differences between participants that dropped out and those that did not?* Yes (specify) Yes, for HRQoL study participants who supplied QoL data were compared to those who had not. The cohort without QoL data were younger, more had experienced an MI and had higher CCS classification	*List of outcomes reported and how they were measured* ETT Exercise duration (seconds) – time from the start of exercise to the beginning of the recovery period Time to ≥ 1-mm ST segment depression(s) – the time from initiation of exercise to the occurrence of horizontal or down-sloping ST segment depression ≥ 1 mm, 80 ms after the J point, persisting for at least three consecutive beats *Angina counts (average frequency of self-reported angina episodes over three 24-hour periods)* The total number of angina episodes reported at three successive treatment sessions divided by the number of days on which the sessions took place. The first three sessions were the baseline period. The difference in angina counts between baseline and end of treatment were calculated as percentage change for each patient, and were classified into categories *NTG count* Average usage of on-demand NTG tablets per day QoL Medical Outcomes Study (SF-36) and the cardiac version of the QLI *Adverse events* Daily questioning by research nurses about any adverse reaction experienced since the previous session

Severe symptomatic peripheral vascular disease History of varicosities, deep vein thrombosis, phlebitis or stasis ulcer, bleeding diathesis Warfarin use with International Normalised Ratio > 2.0 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 Pregnant women and women of childbearing potential	Calcium channel blocker: EECP 44 (62.0); control 36 (54.5) Beta-blocker: EECP 50 (70.4); control 51 (77.3) Lipid-lowering agents: EECP 44 (62.0); control 33 (50.0) NTG usage, mean (SE?) EECP 0.47 (0.13); control 0.51 (0.15) *QoL* Not reported *Other* *Angina years, mean (SD)* EECP 8.56 (7.88); control 4.5 (4.06), $p < 0.01$ *Previous MI* EECP $n = 40$ (56.3%); control $n = 27$ (40.9%), $p < 0.05$ *Previous CABG* EECP $n = 33$ (46.5%); control $n = 25$ (37.9%) *Previous percutaneous transluminal coronary angioplasty* EECP $n = 27$ (38.0%); control $n = 22$ (33.3%), $p > 0.05$ All baseline characteristics based on 71 and 66 participants for EECP and inactive EECP respectively

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

TABLE 13 *Arora* et al., *1999.*[17] *Related papers: Arora* et al., *2002*[22] *reports data on QoL, 12 months after treatment; conference proceedings – summary of QoL subgroup study (continued)*

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 (0.2)

Adjusted mean (SE?): EECP –0.11 (0.21); control 0.1 3 (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_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, $p < 0.05$

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 14 *Barsheshet* et al., *2008*[18]

Methods	Participants	Withdrawals	Outcomes assessed
Non-randomised controlled study *Intervention* EECP 35 hours of EECP over 7 weeks, i.e. 1 hour per day, 5 days per week *Details of any other therapy* All medications, diet and interventions were constant over the 10-week period after the participants were recruited to the study *Comparator* Standard care (not specified) *Details of any other therapy* All medications, diet and interventions were constant over the 10-week period after the participants were recruited to the study *Inclusion criteria* Men and women 40–90 years old Symptomatic coronary artery disease (CAD) documented by previous angiography (> 70% stenosis in any coronary artery) CCS classification II–IV *Exclusion criteria* Unstable angina Acute myocardial infarction in previous 3 months Aortic regurgitation Systemic hypertension > 180/110 mmHg Atrial fibrillation or ventricular premature beats that would interfere with EECP triggering	*Number allocated to each group* EECP $n = 15$; control $n = 10$ *Age [mean (SD)]* EECP 69.8 (11.2); control 69.3 (9.6) *Sex (% male)* EECP 12 (80); control 10 (100) *Race* Not reported *Condition being treated* Stable angina ***Baseline clinical characteristics*** *VO_2 related:* not reported *NYHA classification:* not applicable *CCS classification,* n *(%)* EECP: Class II 2 (13.3); Class III 7 (46.6); Class IV: 6 (40) Control: Class II 2 (20); Class III 5 (50); Class IV 3 (30) *Exercise duration:* not reported *Angina episodes:* not reported *Medication use,* n *(%)* Aspirin: EECP 14 (93.3); control: 9 (90) Beta-blockers: EECP 12 (80); control 7 (70) Statins: EECP 13 (86.6); control 10 (100) Long acting nitrates: EECP 9 (60); control 5 (50) Diuretics: EECP 6 (40); control 4 (40) ACEI/ARB EECP 9 (60); control 7 (70) *QoL:* not reported	*Number of withdrawals and losses to follow-up* None reported *Did study report differences between participants that dropped out and those that did not?* Not applicable	*List of outcomes reported and how they were measured* CCS angina class *Reported but not extracted* 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) Endothelial function – percentage change in flow-mediated dilation after cuff deflation Endothelial dysfunction – asymmetric dimethylarginine, vascular endothelial growth factor and c-reactive protein levels were measured)

Clinically evident peripheral vascular disease Deep vein thrombosis Phlebitis and haemorrhagic diathesis Use of anticoagulants Pregnancy Abdominal aortic aneurysm	*Other* *History of MI*, n *(%)* EECP 12 (80); control 9 (90) *Previous revascularisation (PTCA and/or CABG)*, n *(%)* EECP 14 (93.3); control 10 (100) *Left ventricular ejection fraction, mean* % *(SD)* EECP 51.3 (10.8); control 49.3 (10.9)
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 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.*[21] *Related papers: Abbottsmith* et al., *2006*[137] *report on an additional subgroup analysis of older people; Feldman* et al., *2005*[138] *give details of PEECH trial methodology*

Methods	Participants	Withdrawals	Outcomes assessed
RCT *Intervention* EECP 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 *Details of any other therapy* Continued pharmacotherapy (PT) *Comparator* Continued pharmacotherapy For both groups, patients were receiving heart failure therapy in compliance with the Practice Guidelines of the Heart Failure Society of America For both groups, digoxin, diuretics and other medication used to treat heart failure could be given at the investigators discretion *Inclusion criteria* Symptomatic mild to moderate heart failure (NYHA class II – III) secondary to either ischaemic or non-ischaemic cardiomyopathy and a LVEF ≤ 35% Clinically stable Minimal or no oedema Be receiving heart failure therapy in compliance with the Practice Guidelines of the Heart Failure Society of America before enrolling 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 *Exclusion criteria* Acute coronary syndrome in the 6 weeks prior to enrolment	*Number allocated to each group* EECP *n* = 93; control *n* = 94 *Age [mean (SD)]* EECP 62.4 (11.7); control 63.0 (10.4) *Sex (% male)* EECP 77.4%; control 75.5% *Race* Caucasian: EECP *n* = 76 (81.7%); control *n* = 75 (79.8%) *Condition being treated* Heart failure ***Baseline clinical characteristics*** *VO_2 related* Peak VO_2 ml/kg/minute, mean (SE) EECP 14.7 (0.4); control 14.1 (0.4) (Based on 80 and 84 patients respectively) *NYHA classification,* n *(%)* Class II: EECP 60 (64.5%); control 62 (66%) Class III: EECP 33 (35.5%); control 32 (34.0%) *Exercise duration, seconds, mean (SE)* EECP 610.6 (27.8); control 570.9 (26.1) (Based on 80 and 84 patients respectively) *Medication use* ACE inhibitors, *n* (%): EECP 70 (75.3); control 73 (77.7) Enalapril daily dose equivalent (mg), mean (SD): EECP 11.8 (10.1); control 13.5 (9.9) Median: EECP 10; control 10 Angiotensin-receptor blockers, *n* (%): EECP 18 (19.4); control 18 (19.1) Losartan daily dose equivalent (mg), mean (SD): EECP 63.2 (42.0); control 60.5 (38.5)	*Number of withdrawals and losses to follow-up* EECP *n* = 22 (23.7%) Adverse event: 11 Protocol violation: 2 Refused assignment: 2 Non-compliance: 1 Participant's decision: 5 Loss to follow-up: 2 Other: 4 Control *n* = 13 (13.8%) Adverse event: 3 Protocol violation: 2 Refused assignment: 1 Non-compliance: 0 Participant's decision: 6 Loss to follow-up: 1 Other: 1 *Additional losses to follow-up* EECP: 2 Pharmacotherapy: 1 *Did study report differences between participants that dropped out and those that did not?* No	*List of outcomes reported and how they were measured* Exercise duration – percentage of patients that showed an increase in duration of 60 seconds or more Peak VO_2 – percentage of patients with an increase in peak $VO_2 \geq 1.25$ ml/kg/minute from baseline at 6 months' follow-up Change in peak VO_2 Change in exercise duration Change in ventilatory equivalent for carbon dioxide Change in respiratory exchange ratio Change in Borg Score Change in ventilatory response (l/minute) Change in NYHA functional class Change in QoL (Minnesota Living with Heart Failure Questionnaire) Adverse events (an independent clinical end-points committee classified adverse events)

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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	Median: EECP 50; control 50 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 64 (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)

Results

Exercise duration [mean change in exercise duration from baseline(s) (SE)]

1-week follow-up: EECP ($n = 77$) 26.4 (12.2); control ($n = 78$) –5.5 (11.7), $p = 0.010$

3-month follow-up: EECP ($n = 78$) 34.5 (13.9); control ($n = 82$) –7.0 (12.7), $p = 0.014$

6-month follow-up: EECP ($n = 79$) 24.7 (15.2); control ($n = 83$) –9.9 (13.2), $p = 0.013$

Exercise duration (percentage of patients with at least a 60-second increase in exercise duration from baseline to 6 months' follow-up)

EECP 35.4%; control 25.3%, $p = 0.016$

NYHA classification (% patients with an improvement in NYHA class)

1-week follow-up: EECP 33.3%; control 11.4%, $p < 0.001$

3-month follow-up: EECP 31.6%; control 12.2%, $p < 0.02$

6-month follow-up: EECP 31.3%; control 14.3, $p < 0.01$

CCS classification: not applicable

Angina episodes: not applicable

VO_2 related [mean change in peak VO_2 (ml/kg/minute) (SE)]

1-week follow-up: EECP ($n = 77$) 0.1 (0.3); control ($n = 78$) –0.4 (0.3), $p = 0.071$

3-month follow-up: EECP ($n = 78$) 0.2 (0.3); control ($n = 82$) –0.4 (0.3), $p = 0.119$

6-month follow-up: EECP ($n = 79$) –0.3 (0.3); control ($n = 83$) –0.6 (0.3), $p = 0.315$

VO_2 related (% patients with a peak VO_2 increase ≥ 1.25 ml/kg/minute from baseline to 6 months' follow-up)

EECP 22.8%; control 24.1%, $p = 0.698$

TABLE 15 *Feldman* et al.*, 2006.[21] Related papers: Abbottsmith et al., 2006[137] report on an additional subgroup analysis of older people; Feldman et al., 2005[138] give details of PEECH trial methodology (continued)*

QoL (mean change in QoL score (CIs) 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/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

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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_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_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_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), $p = 0.046$

TABLE 15 *Feldman* et al., *2006.[21] Related papers: Abbottsmith et al., 2006[137] report on an additional subgroup analysis of older people; Feldman et al., 2005[138] give details of PEECH trial methodology (continued)*

Subgroup analysis results
Subgroup 2: Older patients
(EECP $n = 41$; PT $n = 44$)
There were no significant differences at baseline between the subgroup and overall population
Exercise duration – mean change in exercise duration, seconds (variance not reported)
1 week: EECP 23.0, control 3.4, $p = 0.07$; 3 months: EECP 52.2, control –19.1, $p = 0.004$; 6 months: EECP 30.0, control –22.3, $p = 0.001$
Exercise duration – increase in exercise duration ≥ 60 seconds from baseline to 6 months' follow-up
EECP 35.1; control 25%, $p = 0.008$
Improvement in NYHA classification
1 week: EECP 35.1%, control 9.8%, $p = 0.042$; 3 months: EECP 40.5%, control 9.1%, $p = 0.046$; 6 months: EECP 37.8%, control 15.9%, p-value not significant
Peak VO_2 – increase in peak VO_2 ≥ 1.25ml/kg/minute from baseline to 6-month follow-up
EECP 29.7; control 11.4, $p = 0.017$
Mean change in peak VO_2 (from baseline, ml/kg/minute) (variance not reported)
1 week: EECP –0.1, control –0.8, $p = 0.09$; 3 months: EECP 0.3, control –1.1, $p = 0.02$; 6 months: EECP –0.2, control –1.1, $p < 0.001$
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
EECP 12 (29.3%); control 16 (36.4%)
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.

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TABLE 16 *Holubkov* et al., *2002*[19]

Methods	Participants	Withdrawals	Outcomes assessed
Non-randomised controlled study *Intervention* EECP 1–2 hours of treatment per day, 5 or 6 days per week with a minimum total of 35 hours *Details of any other therapy* None reported *Comparator* Elective PCI *Details of any other therapy* None reported *Inclusion criteria* IEPR: all consecutive patients undergoing at least 1 hour of EECP 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 EECP treatment (14.8% of entire cohort) 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)	*Number allocated to each group* EECP $n = 323$; control $n = 448$ *Age [mean (SD)]* EECP 65.7 (10.5); control 64.5 (11.6) *Sex (% male)* EECP 79.9; control 72.3, $p < 0.05$ *Race:* not reported *Condition being treated* Stable angina ***Baseline clinical characteristics*** *VO_2 related:* not reported *NYHA classification:* not applicable *CCS classification* EECP: Class I 9.6%; Class II 26.0%; Class III 47.1%; Class IV 17.3% Control: Class I 5.3%; Class II 41.4%; Class III 48.3%; Class IV 5.1%. $p < 0.001$ *Exercise duration:* not reported *Angina episodes:* not reported *Medication use:* not reported *QoL*: not reported *Other* *Prior PCI* EECP 53%; control 33.3%, $p < 0.001$ *Prior CABG* EECP 42.1%; control 18.6%, $p < 0.001$ *Prior MI* EECP 56.4%; control 27.8%, $p < 0.001$ *Congestive heart failure* EECP 16.8%; control 9.2%, $p < 0.01$ *LVEF* EECP 50.3 (SD 10.8); control 59.2 (SD 12.6), $p < 0.001$	*Number of withdrawals and losses to follow-up* Loss to follow-up unclear Patients alive and contacted at follow-up: EECP $n = 251$; control $n = 422$ *Did study report differences between participants that dropped out and those that did not?* No	*List of outcomes reported and how they were measured* All-cause mortality Self-reported exertional angina CCS classification Medication use PCI during follow-up Repeat EECP (EECP group only) With the exception of mortality, outcomes were based on phone interview or by mail

TABLE 16 *Holubkov et al., 2002[19] (continued)*

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

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TABLE 17 *Shechter* et al., *2003*[20]

Methods	Participants	Withdrawals	Outcomes assessed
Non-randomised controlled study *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	*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 ***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	*Number of withdrawals and losses to follow-up* None *Did study report differences between participants that dropped out and those that did not?* Not applicable	*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

TABLE 17 *Shechter* et al., *2003*[20] *(continued)*

Clinically evident peripheral vascular disease Deep vein thrombosis Phlebitis and haemorrhagic diathesis Use of anticoagulants Pregnancy Abdominal aortic aneurysm History of drug or alcohol abuse Chronic liver disease	*Other* *Body mass index (kg/m²), mean (SD):* EECP 26 (4); control 25 (7) *Systemic hypertension,* n *(%):* EECP 10 (50); control 7 (35) *Previous MI,* n *(%):* EECP 14 (70); control 13 (65) *Previous coronary angioplasty, n (%):* EECP 12 (60); control 13 (60) *Previous coronary bypass, n (%):* EECP 10 (50); control 11 (55)
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 *VO_2 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

	Manufacturer's study[24]	
	Grade	**Comments**
Study question		
1. Costs and effects examined	Yes	
2. Alternatives compared	Yes	
3. The viewpoint/perspective of the analysis is clearly stated (e.g. NHS, society)	Yes	US payer's perspective
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing, if applicable)	Yes	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often?)	Yes	
6. The rationale for choosing the alternative programmes or interventions compared is stated	Yes	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Yes	
10. Effectiveness data from RCT or review of RCTs	No	Effectiveness data derived from registry data and observational studies. No RCT data were available for the alternatives being compared
11. Potential biases identified (especially if data are not from RCTs)	No	
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)	NA	No formal synthesis was undertaken
Costs		
13. All the important and relevant resource use is included	Yes	
14. All the important and relevant resource use is measured accurately (with methodology)	Yes	
15. Appropriate unit costs estimated (with methodology)	Yes	
16. Unit costs reported separately from resource use data	No	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Yes	2004 US dollars

	Manufacturer's study[24]	
	Grade	**Comments**
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	
20. Methods to value health states and other benefits are stated	No	No health states were valued
21. Details of the individuals from whom valuations were obtained are given	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Yes	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Yes	
24. All model outputs described adequately	Yes	
Discounting		
25. Discount rate used for both costs and benefits	Unclear	Costs were discounted at 3% per year. Not clear whether benefits were discounted
26. Do discount rates accord with NHS guidance?	No	NHS guidance recommends 3.5% per year for costs and benefits
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around ICER, cost-effectiveness acceptability curves)	NA	
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)	NA	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	No	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	No	
32. Are the probability distributions adequately detailed and appropriate?	No	
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)	No	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	Yes	One-way sensitivity analysis
35. The choice of variables for sensitivity analysis is justified	Yes	
36. The ranges over which the variables are varied are stated	Yes	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	Yes	
38. Major outcomes are presented in a disaggregated as well as an aggregated form	Yes	
39. Applicable to the NHS setting	No	US based and unclear how generalisable these results are to a UK setting

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 non-linear, 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).

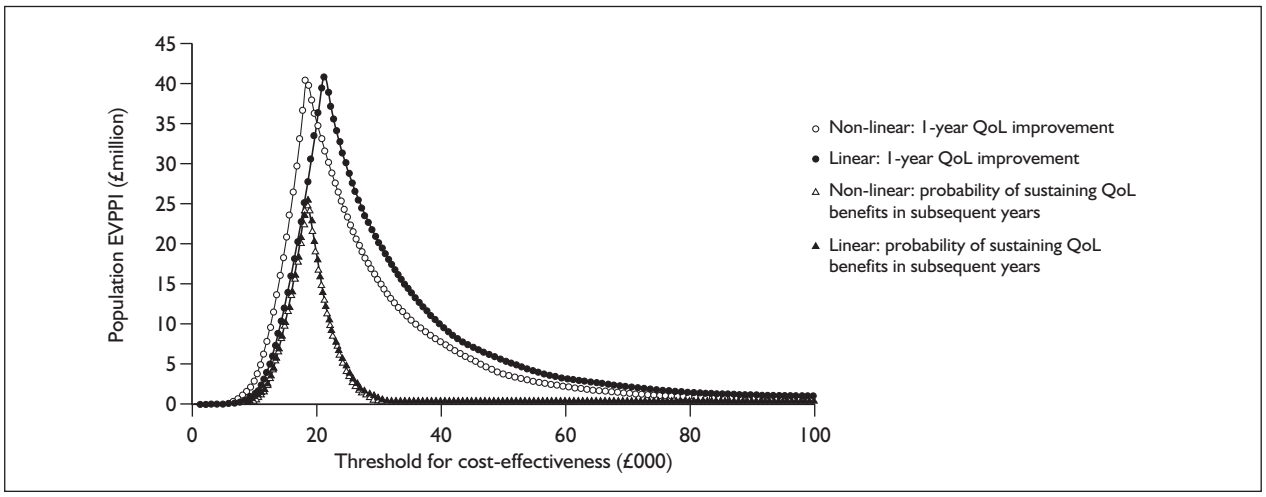


FIGURE 11 *Expected value of perfect information for parameters: linear assumption versus non-linear estimate.*

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.

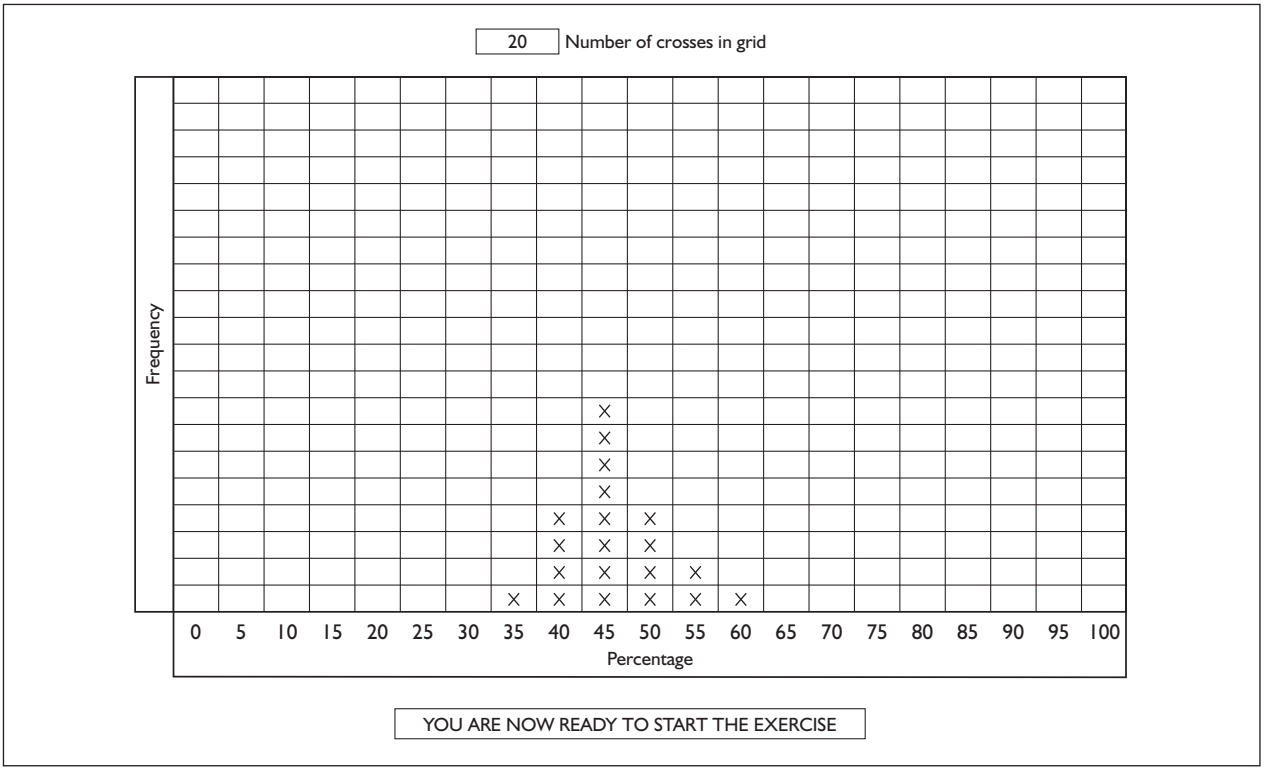


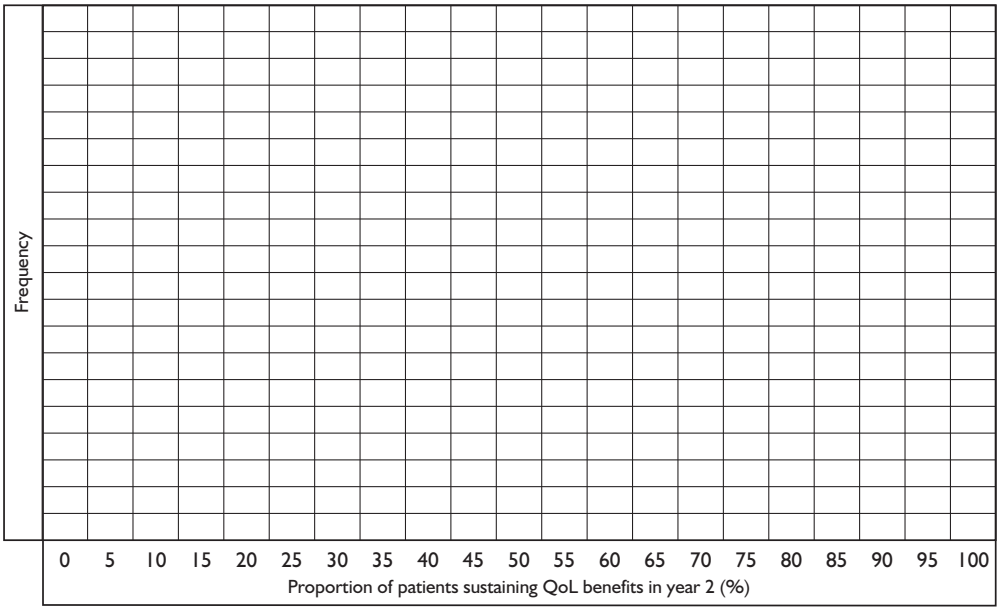
FIGURE 12 *Example grid.*

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



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

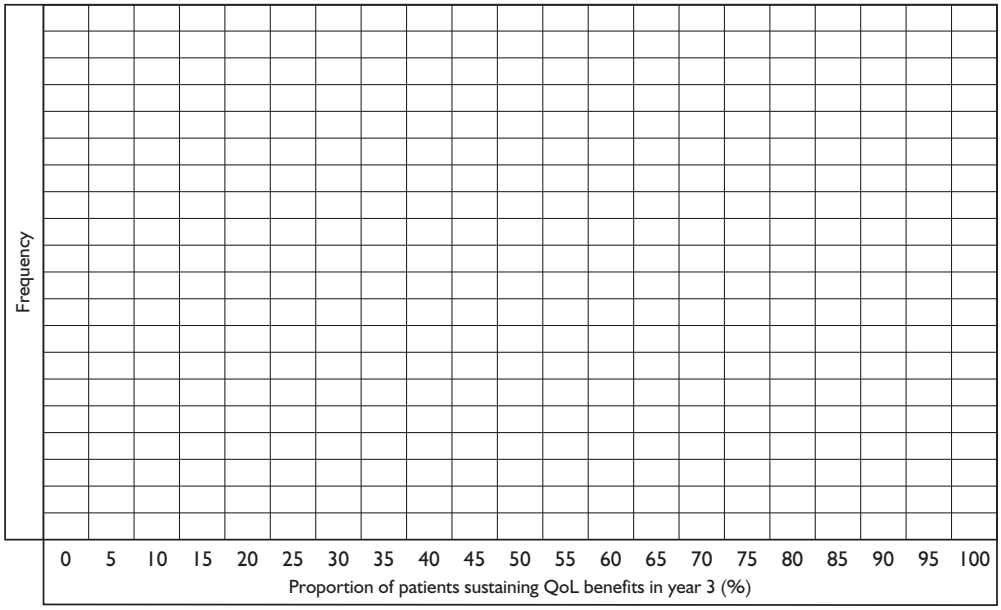
YES ❑ Please continue to Question 2 on the next page.

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 ❑ Please continue to Question 3 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.

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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
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Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
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A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
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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 HSJ, 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.

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Systematic review of treatments for atopic eczema.
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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.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, 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.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

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The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

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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, Ashtead

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 Patnick, 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 Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, 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

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.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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