The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model

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Executive summary

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Background
Heart failure is a major cause of morbidity and mortality in Western societies. It is associated with poor life expectancy, poor quality of life and some of the highest costs for healthcare from a single condition. Heart failure can result from a number of causes, but this report is concerned with that caused by left ventricular systolic dysfunction in which the left lower chamber of the heart fails to pump in synchrony with some or all of the other chambers of the heart. This results in inefficient pumping of blood around the body. The symptoms and signs of heart failure are primarily managed by medication. However, as the condition becomes more severe, the person with heart failure may no longer respond to such treatment.

Cardiac resynchronisation therapy (CRT), also referred to as biventricular pacing, aims to improve the pumping efficiency of the heart by resynchronising the pumping action of the heart’s chambers. A CRT device (CRT-P) consists of a pulse generator implanted in the upper chest from which three leads descend into the heart. The leads are placed (a) in the upper and lower chambers on the right side of the heart and (b) the third lead is directed, via a blood vessel, round the outside of the left lower chamber of the heart. An implantable cardioverter defibrillator (ICD) can be included with the pulse generator to defibrillate the heart internally if an acute arrhythmic event should ensue (CRT-D).

Objectives
The purpose of this report is to assess the clinical effectiveness and cost-effectiveness of CRT for people with heart failure and evidence of dyssynchrony by comparing CRT-P and CRT-D devices each with OPT, and with each other.

Methods
Clinical effectiveness and cost-effectiveness systematic reviews
Electronic databases were searched for relevant published literature on the clinical effectiveness and cost-effectiveness of CRT for heart failure. Studies comparing CRT and automatic ICDs alone were deemed outside the scope of this report. Updated searches were undertaken in June 2006. Included randomised controlled trials (RCTs) were critically appraised for internal and external validity. Relevant data were extracted, narrative reviews were undertaken and meta-analyses of the clinical trial data were conducted. The manufacturers’ submissions to NICE were searched for additional evidence.

PenTAG cost–utility model
A Markov model was developed to address the NICE project scope and protocol. The model compared CRT-P and CRT-D with optimal pharmaceutical therapy (OPT) and with the alternative device, that is, CRT-P versus CRT-D. Ultimately, however, the results for CRT-D versus OPT were thought to be much less relevant to the decision problem, and the results from this comparison are accordingly given less attention. Clinical effectiveness parameters in the model were derived from the systematic review and other published sources. Resource use and costs associated with CRT and treating heart failure in the UK NHS were based on a mixture of published sources, unpublished sources and expert clinical advice. A simulated cohort of 1000 people of mixed age and mixed sex was modelled until the whole cohort was dead. Incremental costs and quality-adjusted life-years (QALYs) were calculated. Extensive one-way sensitivity analyses, threshold analyses, probabilistic sensitivity analyses and value of information analyses were carried out.

Results
Number and quality of studies
Five RCTs met the inclusion criteria, recruiting a total of 3434 participants. Four studies compared CRT-P with OPT, two studies compared CRT-D with OPT and one study compared CRT-P with CRT-D. In all trials, patients with an indication for an ICD were excluded. Studies were of good to moderate quality. Two trials reported that allocation to treatment group had been concealed (CARE-HF and MIRACLE), blinding occurred in three trials (CONTAK-CD, MUSTIC-SR and
MIRACLE) and intention-to-treat was used in four analyses (CARE-HF, COMPANION, MIRACLE and MUSTIC-SR).

### Summary of benefits and risks

Meta-analyses showed that both CRT-P and CRT-D devices significantly reduced the mortality and level of heart failure hospitalisations. They also improved health-related quality of life in people with New York Heart Association (NYHA) class III and IV heart failure and evidence of dysynchrony (QRS interval >120 ms) who were also receiving OPT. A single direct comparison (COMPANION) indicated that the effects of the CRT-P and CRT-D were similar, with the exception of an additional reduction in sudden cardiac death (SCD), associated with CRT-D. On average, implanting a CRT device in 13 people would result in the saving of one additional life over a 3-year period, compared with OPT.

There were no statistically significant subgroup effects, although trials were not individually powered for their detection.

A number of adverse events were associated with the CRT devices. The overall complication rate was 14%, mostly lead related. In addition, there were 0.8% perioperative deaths and 9% failure to implant the device. Of heart failure patients, 11–46% fail to benefit from CRT, clinical parameters suggesting a lower rate of failed response than echocardiographic measures.

### Summary of costs

The NHS device and procedure cost of implanting a new CRT-P system (pulse generator unit and required leads) was estimated to be £5074, and that of a CRT-D system £17,266. Additional costs will be incurred for replacement devices at a mean time interval of 6.5 years for CRT-P and 5.5 years for CRT-D. The discounted lifetime costs of OPT, CRT-P and CRT-D (including the cost of periodic unit replacements, treatment for complications and potential implant with an ICD) were estimated as £9375, £20,804 and £32,689, respectively.

### Summary of cost-effectiveness

Six studies were identified that met our criteria. However, none were from a British society or UK NHS perspective. The evaluations showed that the cost-effectiveness of CRT increases as the time horizon lengthens.

Industry submissions to NICE contained four cost-effectiveness analyses, of which two were more appropriate as reference cases for this report. One, based mainly on the European CARE-HF trial but using resource use data from a UK hospital, used a discrete event simulation model. This gave estimated incremental cost-effectiveness ratios (ICERs) of £15,645 per QALY for CRT-P versus OPT. The other analysis was based on the results of the COMPANION trial, but substituted UK-based hospital unit costs for those originally based on US-defined diagnostic related groups. They estimated an ICER of £2818 per QALY gained by CRT-P versus OPT and a cost per QALY gained of £22,384 for CRT-D versus OPT. Neither of these analyses had time horizons that would adequately include the periodic cost of unit or device replacements (e.g. due to battery depletion), and neither directly compared the cost-effectiveness of CRT-D with CRT-P.

Compared with OPT, the PenTAG Markov model base case analysis (over a lifetime) estimated that CRT-P conferred an additional 0.70 QALYs for an additional £11,630 per person, giving an estimated ICER of £16,735 per QALY gained for a mixed age cohort (range £14,630–20,333). CRT-D versus CRT-P conferred an additional 0.29 QALYs for an additional £11,689 per person, giving an ICER of £40,160 per QALY for a mixed age cohort (range £26,645–59,391).

The PenTAG ICERs are higher than those from the industry-submitted analyses. These differences are due to the industry analyses having higher estimated QALYs and failing to include the costs incurred from repeated replacement of devices, due to modelling the decision over 5 years.

### Sensitivity analysis

One-way sensitivity analyses showed that the PenTAG model was sensitive to model time horizon, device lifetime, discount rate applied to health benefit, probability of a major arrhythmic event, risk of sudden cardiac death and the risk of death from worsening heart failure.

Probabilistic sensitivity analysis based on 1000 simulated trials showed that, at a willingness-to-pay (WTP) threshold of £30,000 per QALY:

- CRT-P versus OPT: CRT-P was likely to be cost-effective in 91.3% of simulations and CRT-P was negatively dominated (i.e. the more you pay, the less quality of life you receive) in 0.4% of simulations.
- CRT-P versus CRT-D: CRT-D was likely to be cost-effective in 26.3% of simulations and CRT-P dominated CRT-D in 7.8% of simulations.
The relative risk for risk of sudden cardiac death when CRT-D is compared with OPT is 0.44 in the base case. This treatment becomes cost-ineffective, at a WTP threshold of £30,000 when this value is greater than 0.65.

When both CRT-P and CRT-D were considered as competing technologies with each other and OPT (three-way probabilistic analysis), and at the same WTP threshold, there was a 68% probability that CRT-P provided the highest expected net benefit. The WTP threshold would need to be above £40,000 before CRT-D provided the highest expected net benefit.

Discussion
For people implanted with the CRT-P device, the risk was reduced for all-cause mortality and hospitalisation for heart failure during up to 3 years of follow-up. For those implanted with a CRT-D device, the risks of all-cause mortality, sudden cardiac death and cardiac death were reduced during up to 16 months of follow-up. Based on limited clinical evidence, both devices significantly improved exercise capacity, health-related quality of life and NYHA class, at 3–6 months. Comparison of outcomes between CRT-P and CRT-D showed no significant differences, with the exception of sudden cardiac death, which was lower with CRT-D. No statistically significant difference in CRT effects was seen across our predefined subgroups.

Adverse events were reported inconsistently. However, CRT appears to be a relatively safe procedure with a low risk of perioperative and postoperative complications, at least up to 3 years’ follow-up.

The cost-effectiveness of CRT appears to be dependent on the time horizon of the analysis and follow-up, cost-effectiveness improving with increasing time horizon and therefore greater extrapolation beyond the trial duration.

Strengths, limitations of the analyses and uncertainties
The strengths of this systematic review and economic evaluation are that it is comprehensive, systematic, up to date and independent.

The limitations of the clinical systematic review were that evidence directly comparing CRT-P with CRT-D was limited, follow-up times were short (three trials 6 months, one trial 15 months, one trial 36 months) and the studies were not sufficiently powered for subgroup analyses. People with atrial fibrillation or an indication for an ICD were excluded from the studies.

The main limitation of the review of economic evaluations, for our purposes, was that none of the studies were from a UK NHS or British society perspective.

The submission from industry was based on European and US trials and case series data from a UK hospital. CRT-P was not compared with CRT-D.

Generalisability of the findings
The populations in the included trials may not be fully representative of the general population of people with heart failure in UK; typically, the trial populations were younger and had less co-morbidity. In addition, none of the trials included in this systematic review included people with conventional indications for an ICD.

Conclusions
In the population considered in this review, CRT-P and CRT-D devices reduce mortality and hospitalisations due to heart failure, improve quality of life and additionally CRT-D devices reduce sudden cardiac death in people with heart failure NYHA classes III and IV, in sinus rhythm with QRS >120 ms.

When measured using a lifetime time horizon and compared with optimal medical therapy, the devices (CRT-P ICER £16,735, CRT-D ICER £23,650) are estimated to be cost-effective at a WTP threshold of £30,000 per QALY, CRT-P is cost-effective at a WTP threshold of £20,000 per QALY.

When the cost and effectiveness of all three treatment strategies are compared with each other, the estimated net benefit from CRT-D is less than with the other two strategies, until the WTP threshold exceeds £40,160/QALY.

Implications for service provision
The rate of implanting CRT devices in UK is currently increasing by about 50% per annum. There are consequent implications for the training of cardiologists and related clinical staff and the adequate provision of implantation centres and associated diagnostic infrastructure.
Recommendations for future research
The following areas are suggested for further research.

- Prediction of non-responders: systematic reviews of current evidence and further primary studies are needed in this area.
- Appropriate use of CRT-D devices: only the COMPANION study directly compared CRT-P and CRT-D devices. The question remains as to which group of heart failure people should receive a CRT-D device.
- NYHA classes I and II: RCTs powered to detect differences in mortality and heart failure hospitalisation are needed.
- Long-term safety data: observational studies are needed to determine the long-term safety of CRT devices.

- Based on the expected value of perfect parameter information analysis, studies with long-term follow-up are needed to provide a better understanding of the different modes of death in people with a CRT device and also those receiving OPT. The results indicate that information about all hazard ratios would give the maximum reduction in decision uncertainty.

Publication
The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care. The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

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

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

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

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

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

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

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors. Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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

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