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

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Abstract

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

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Objectives: To assess the clinical effectiveness and cost-effectiveness of cardiac resynchronisation therapy (CRT) for people with heart failure and evidence of dyssynchrony by comparing cardiac resynchronisation therapy devices, CRT-P and CRT with defibrillation (CRT-D), each with optimal pharmaceutical therapy (OPT), and with each other.

Data sources: Electronic databases were searched up to June 2006. Manufacturer submissions to the National Institute for Health and Clinical Excellence (NICE) were also searched for additional evidence.

Review methods: Relevant data from selected studies were extracted, narrative reviews were undertaken and meta-analyses of the clinical trial data were conducted. A Markov model was developed. 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: Five randomised controlled trials met the inclusion criteria, recruiting 3434 participants. Quality was good to moderate. Meta-analyses showed that both CRT-P and CRT-D devices significantly reduced the mortality and level of heart failure hospitalisations and they improved health-related quality of life in people with New York Heart Association (NYHA) class III and IV heart failure and evidence of dyssynchrony (QRS interval >120 ms) who were also receiving OPT. A single direct comparison indicated that the effects of 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. 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. The discounted lifetime costs of OPT, CRT-P and CRT-D were estimated as £9375, £20,804 and £32,689, respectively. The industry submissions to NICE contained four cost-effectiveness analyses, of which two were more appropriate as reference cases. One used a discrete event simulation model that gave estimated incremental cost-effectiveness ratios (ICERs) of CRT-P vs OPT of £15,645 per QALY. The other analysis was based on the results of the COMPANION trial and estimated an ICER of £2818 per QALY gained by CRT-P vs OPT and a cost per QALY gained of £22,384 for CRT-D vs OPT. Compared with OPT, the Markov model base case analysis 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 vs 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 authors' ICERs are higher than those from the industry-submitted analysis. Probabilistic sensitivity analysis based on 1000 simulated trials showed that, at a willingness-to-pay (WTP) threshold of £30,000 per QALY, in CRT-P versus OPT, CRT-P was likely to be cost-effective in 91.3% of simulations and that CRT-P was negatively dominated in 0.4% of simulations. It also showed that in CRT-P versus CRT-D, CRT-D was likely to be cost-effective in 26.3% of simulations and that CRT-P dominated CRT-D in 7.8% of simulations. The relative risk for SCD 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, 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.

Conclusions: The study found that CRT-P and CRT-D devices reduce mortality and hospitalisations due to heart failure, improve quality of life and reduce SCD in people with heart failure NYHA classes III and IV, and evidence of dyssynchrony. When measured using a lifetime time horizon and compared with optimal medical therapy, the devices 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, the estimated net benefit from CRT-D is less than with the other two strategies, until the WTP threshold exceeds £40,160/QALY. Further research is needed into the identification of those patients unlikely to benefit from this therapy, the appropriate use of CRT-D devices, the differences in mortality and heart failure hospitalisation for NYHA classes I and II, as well as the long-term implications of using this therapy.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Angiography A radiographic technique where a radiopaque (shows up on X-ray) contrast material is injected into a blood vessel for the purpose of identifying its anatomy on X-ray

Arrhythmia Any variation from the normal rhythm of the heart beat

Atrial fibrillation A condition where there is disorganised electrical conduction in the atria, resulting in ineffective pumping of blood into the ventricle

Cardiomyopathy A general diagnostic term denoting primary heart disease

Echocardiography A diagnostic test which uses ultrasound to visualise the structure and function of the heart

Electrocardiogram (ECG) A recording of the electrical activity of the heart on a moving strip of paper

External validity The extent to which the results of a trial provide a correct basis for applicability to other circumstances

Internal validity The extent to which systematic error is minimised in a clinical trial

Ischaemic heart disease A disorder of cardiac function caused by insufficient blood flow to the muscle of the heart

Left ventricular ejection fraction The amount of blood ejected from the left ventricle during a single beat expressed as a percentage

Left ventricular systolic dysfunction A loss of the normal pumping action of the left ventricle

Myocarditis An inflammation of the muscular walls of the heart

Natriuretic peptide test (or BNP) A measurement of a protein in the blood which may be used to diagnose heart failure

QRS complex The deflections in an ECG tracing that occur during ventricular contraction

Radionuclide ventriculography A test that uses radioactive materials called tracers to make heart chambers and blood vessels visible

Syncope A temporary loss of consciousness due to inadequate blood flow to the brain

List of abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndromes
ACE	angiotensin-converting enzyme
AF	atrial fibrillation
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
BiVP	biventricular pacing
BNF	British National Formulary
BNP	B-type natriuretic peptide
BVP	biventricular pacing
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness frontier
CHF	congestive heart failure
CI	confidence interval
CrI	credibility interval
CRT	cardiac resynchronisation therapy
CUA	cost–utility analysis
DRG	Diagnosis Related Group
ECG	electrocardiogram
ECHO	echocardiography
EF	ejection fraction
ESC	European Society of Cardiology
ESVI	end-systolic volume index
EVPI	expected value of perfect information
EVPPI	expected value of perfect parameter information
FDA	Food and Drugs Administration
GFR	glomerular filtration rate
HF	heart failure
HR	hazard ratio
HRG	healthcare resource group
ICD	implantable cardioverter defibrillator
ICER	incremental cost-effectiveness ratio
IMD	Index of Multiple Deprivation
IQR	interquartile range
ITT	intention-to-treat
LBBB	left bundle branch block
LVDD	left ventricular diastolic diameter
LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVSD	left ventricular systolic dysfunction
MI	myocardial infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MLWHF	Minnesota Living with Heart Failure
NICE	National Institute for Health and Clinical Excellence
NSIVCD	no specific intraventricular conduction delay
NSRC	National Schedule of Reference Costs
NT-BNP	plasma N-terminal brain natriuretic peptide
NYHA	New York Heart Association
OPT	optimal pharmaceutical therapy
PASA	Purchasing and Supplies Agency
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
QRS	second wave on ECG recording electrical activity of ventricles
RBBB	right bundle branch block
RCT	randomised controlled trial
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SD	standard deviation
TAR	technology assessment review
TDI	tissue Doppler imaging
VDI	virtual device interface
VF	ventricular fibrillation
VT	ventricular tachycardia
WTP	willingness-to-pay

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 at the end of the table.

Executive summary

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 dyssynchrony (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.

Chapter 1
Background

Description of health problem

Heart failure (HF) is a clinical syndrome caused by a reduction in the heart's ability to pump blood around the body; this can be due to structural or functional reasons. It is one of the major causes of morbidity and mortality in Western societies with increasingly ageing populations. HF is linked to a poor outlook, poor quality of life (QoL) and to some of the highest costs for healthcare from a single disease.[1,2]

Aetiology

The most common cause of HF in the UK is ischaemic heart disease. A history of hypertension or atrial fibrillation is also common.[3] Other causes of HF include cardiomyopathy, valve disease and myocarditis. Idiopathic cardiomyopathy accounts for just under 15% of cases under the age of 75 years.[4]

Diagnosis

There is no single diagnostic test for HF. Diagnosis relies on clinical judgement based on a combination of history, physical examination and appropriate investigations.[5] Heart failure may be suspected from a chest X-ray, an ECG or elevation in plasma B-type natriuretic peptide (BNP) levels. The diagnosis of HF should be accompanied by an objective evaluation of cardiac function, using echocardiography (ECHO), radionuclide ventriculography, fluoroscopic ventriculography or cardiac magnetic resonance imaging.

The reduction in cardiac function is commonly assessed by measurement of the left ventricular ejection fraction (LVEF). This is the amount of blood ejected from the left ventricle during a single beat expressed as a percentage.

A broad QRS complex on the ECG is often taken as a surrogate marker of uncoordinated ventricular contraction.

Pathology

HF can result from a range of cardiovascular disorders. HF due to left ventricular systolic dysfunction (LVSD) is the subject of this report, and occurs as the result of the loss of normal functioning of the ventricles of the heart. The ventricles should pump in synchrony with the heart's upper chambers (atria). If the contractions lack synchrony, either within or between the ventricles, or between the atria and ventricles, the heart becomes less efficient as a pump. The central problem is delay in activation of the left ventricle, since this reduces the efficiency of an already damaged pump. Such LVSD is a marker of heart failure. Once it has occurred, the heart tries to compensate for the loss of function by producing structural changes which effect a remodelling of the tissue of the left ventricle.

Symptoms

HF is characterised by symptoms such as breathlessness, reduced exercise tolerance, fatigue and fluid retention, together with signs of reduced cardiac output.[3] These characteristics may be exacerbated by any dys-coordination in ventricular contraction pattern, the lack of synchrony in the beating of the ventricles due to delay in the onset of ventricular contraction and the reduced ability of the heart muscle to contract.[6] This reduction in the force of contraction, coupled with coordinate contraction, will reduce cardiac output and may increase the quantity of regurgitant flow through the mitral valve.[7]

Such intraventricular conduction abnormalities are found in about 30% of people with moderate to severe HF.[8]

Symptoms of HF can be described using the New York Heart Association (NYHA) classification:

- **Class I**: No limitations. Ordinary physical activity does not cause fatigue, breathlessness or palpitation (asymptomatic left ventricular dysfunction is included in this category).
- **Class II**: Slight limitation of physical activity. Such people are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, breathlessness or angina pectoris (symptomatically 'mild' heart failure).
- **Class III**: Marked limitation of physical activity. Although people are comfortable at rest, less than ordinary physical activity will lead to symptoms (symptomatically 'moderate' heart failure).

- **Class IV**: Inability to carry on any physical activity without discomfort. Symptoms of congestive cardiac failure are present even at rest. With any physical activity increased discomfort is experienced (symptomatically 'severe' heart failure).

Prognosis

The national UK horizon scanning centre reports that HF has a poor prognosis, with just under 40% of patients dying within 1 year of diagnosis,[9] Patients with HF are susceptible to sudden cardiac death (SCD).[10] It is difficult to determine the death rate from HF because of the way in which death is reported in the UK, where the 4% of deaths recorded as due to HF are an underestimate if HF is regarded as a cause of death rather than a mode of death.[11] One-year survival in a survey in Hillingdon, London, in 1995 was 62% (comparable to colonic cancer but less favourable than current breast, prostate or bladder cancer survival rates), with a mortality rate after the first year of around 8–10% per year.[12]

Epidemiology

Incidence and prevalence

About 900,000 people in England and Wales have HF, of whom at least half have LVSD.[13] People with LVSD tend to be younger than the general UK population of people with heart failure.[1] Annual mortality (within this population) due to severe HF is around 60%.[1]

Incidence and prevalence of HF increase steeply with age, with the average age at first diagnosis being 76 years.[12] While around 3% of people aged 65–74 years have HF, this increases to about 7% of those aged 75–84 years and to just over 14% in those aged 85 years and above.[1] The risk of HF is higher in men than in women in all age groups,[1] but there are more women than men with heart failure due to demographics.[13]

The European Society of Cardiology (ESC) estimates the crude incidence of HF in the UK to be 140/100,000 in men and 120/100,000 in women. Although incidence is higher in men, evidence suggests higher mortality in women with the condition.[14]

Prevalence figures for people over the age of 65 years with HF in the UK are 40/1000 in men and 30/1000 in women.[15] In Davies' Heart of England screening study,[1] figures for the prevalence of probable HF of 0.8% [ejection fraction (EF) 40–50%] and definite HF of 2.3% (EF <40%), give an overall prevalence of HF in the general population of England of 3.1%. Of those with definite HF (2.3%), defined as an EF <40%, 47% were asymptomatic. When definite cases of HF are considered according to the NYHA classification, 27% are in class I, 50% in class II, 11% in class III and 12% in class IV[1] (*Figure 1*).

The National Institute for Health and Clinical Excellence (NICE) Guideline for Chronic Heart Failure (2003) asserts that:

> "On average, a general practitioner will look after 30 patients with heart failure, and suspect a new diagnosis of heart failure in perhaps 10 patients annually. Those who work in more deprived areas are likely to have more cases. The cost of general practitioner consultations has been estimated at £45 million per year, with an additional £35 million for GP referrals to outpatient clinics. In addition,

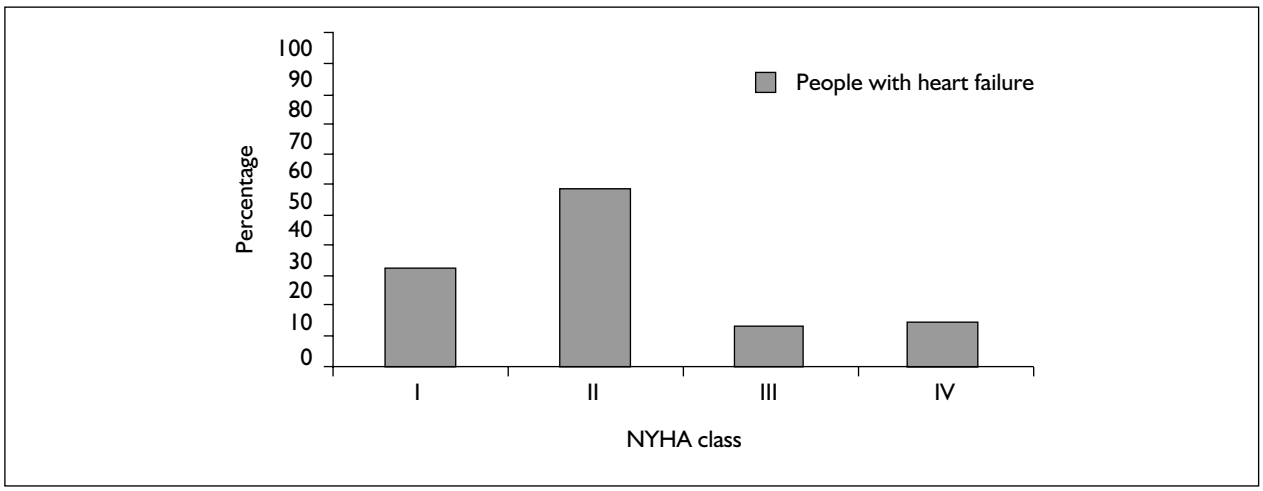

FIGURE 1 *Distribution of heart failure in England 2001 according to the NYHA classification[1]*

> community-based drug therapy costs the NHS around £129 million per year.[16,17] Heart failure accounts for a total of 1 million inpatient bed days – 2% of all NHS inpatient bed days – and 5% of all emergency medical admissions to hospital. Hospital admissions due to heart failure are projected to rise by 50% over the next 25 years – largely due to the ageing of the population."[5]

It is estimated that 20–30% of people with NYHA class III/IV chronic HF have sufficiently low LVEF and prolonged QRS duration to be potential candidates for CRT.[18] In 2003, this was estimated to constitute between 4200 and 8400 people in England and Wales.[19] However, a more recent cohort study reduces this estimate to 1–3% of those discharged from hospital for heart failure in NYHA classes III/IV.[20]

Studies of the prevalence of HF in England and Wales show a wide range of prevalence across ages; estimates within age categories are relatively consistent across studies, from 0.3 to 10.4% for men and from 0 to 13.3% for women[1,21–23] (see *Table 1*).

Impact of health problem

Significance for patients in terms of ill-health – quality of life

The burden for people with HF is both financial and on their diminishing QoL and reduced life expectancy.

The financial costs incurred include prescription charges (in patients under 60 years old), costs associated with attending GP surgeries, outpatient clinics, stays in hospital, loss of earnings (both their own and those of family carers) and modifications to the home.

HF reduces QoL. Participants in the Echocardiographic Heart of England Screening study who completed the SF-36 questionnaire[24] (n = 5961), showed that people with HF had a significantly poorer QoL in all aspects than those without HF. In particular, the physical health burden was greater than those with other chronic disorders.[25]

People with HF have a significantly reduced QoL compared with a healthy population, showing a similar pattern to those on chronic haemodialysis.[26] This is due to the physical limitations of the disease and the ensuing social limitations with emotional problems. These issues can be caused by the disease itself, co-morbidities or the effects of treatment.[27] People with moderate to severe HF are also more likely to suffer from depression.[26]

Significance for the NHS

The cost of HF to the NHS is estimated to be 1.8% of the total budget, of which approximately 66% comes from hospital admissions.[16,28,29] HF is the cause of about 5% of UK hospital medical admissions.[2] Hospital episodes data suggest an average stay of 9 days for patients with HF. In the UK in 2000, HF costs an estimated £628.6 million per annum.[30] Of those who survive their first admission, one-third will die in the subsequent year.[31] The number of people with HF is increasing due to the increasingly elderly population and the improved survival of those with coronary artery disease. The costs of HF increase with disease severity, with the healthcare costs for patients with the most severe symptoms being 8–30 times greater than those with mild symptoms.[32]

Measurement of disease

HF and its consequences are measured in a variety of ways.

1. LVEF. This is the amount of blood ejected from the left ventricle expressed as a percentage of the total volume. It is only one global measure of cardiac function. The LVEF is usually assessed by ECHO.
2. QRS duration. This is a measure of the time taken for electricity to flow through both ventricles and is derived from the surface ECG. A broad QRS signal correlates with advanced HF and a higher risk of SCD.
3. Exercise capacity. Exercise tolerance can be assessed in a number of ways, including a treadmill or 6-minute walk test, and may include additional measures that allow the prediction of myocardial oxygen uptake. The 6-minute walk test has been shown to be a reliable and valid test in heart failure which is predictive of morbidity and mortality.[33,34]
4. BNP. Elevated plasma levels of BNP are a marker for left ventricular dysfunction.[35]
5. NYHA living with heart failure class. This is a subjective, self-report measure of functional ability on a scale ranging from I to IV (mild to severe)[36] (see the section 'Symptoms', p. 1, for details of the scale). It has been shown to be reliable and valid when correlated with objective measures, and has demonstrated a moderate correlation with peak oxygen flow (VO_2 max.), exercise capacity.[37] However, it should be noted that a person's self-rating status on this measure can vary in both directions over a short period.
6. The Minnesota Living with Heart Failure (MLWHF) questionnaire. This contains 21

TABLE 1 *Prevalence of heart failure, adults aged 45–84 years: UK studies compared*

Year	Place	No. in study	Men (%)				Women (%)			
			45–54 years	55–64 years	65–74 years	75–84 years	45–54 years	55–64 years	65–74 years	75–84 years
1991–92	England and Wales[21]			0.5[a]	3.2	8.0		0.4[a]	2.3	7.1
1994	Liverpool[22]	17,400		2.7	5.3	10.4[b]		1.2	5.1	13.3[b]
1998	England and Wales[23]	1,400,000	0.3	1.4	4.5	10.9	0.2	0.9	3.6	9.9
1995–99	West Midlands[1]	3,960	0.3	2.7	4.2	7.3	0	0.9	1.7	6.6

[a] For those aged 45–64 years.
[b] For those aged 75 years and over.
Source: British Heart Foundation, 2006.[15]

items, addresses a wide range of health-related QoL aspects and is a reliable and valid measure of HF when correlated with objective measures.[38] The MLWHF questionnaire was developed in 1984 to measure the effects of HF and treatments for HF on an individual's QoL.[39] The content of the questionnaire was selected to be representative of the ways in which HF and treatments can affect the key physical, emotional, social and mental dimensions of QoL without being too long to administer during clinical trials or practice. Care should be taken in its interpretation as there may be individual and cultural variations in the way in which the functional limitations experienced due to HF are interpreted.

Current service provision

Management of disease

Lifestyle

NICE guidance for HF recommends that people with HF should be encouraged to adopt regular aerobic and/or resistive exercise, possibly as part of a programme of exercise or rehabilitation, and that they also give up smoking. Although excessive alcohol consumption may damage cardiac muscle,[40] there is no evidence that moderate consumption does any obvious harm unless HF is alcohol related.[41] Lack of research about the effects of diet and nutrition on HF mean that advice is limited beyond reducing salt intake to control fluid retention.[5] This guidance is echoed by the ESC, which states in its recommendations that people with HF should be encouraged to carry out activities that do not induce symptoms.[42]

Pharmacological therapy

The NICE Chronic Heart Failure Guideline 2003[5] states that a large majority of patients with HF will require drug therapy; these include:

- Angiotensin-converting enzyme (ACE) inhibitors, which are recommended for all patients with LVSD to improve ventricular geometry and function.
- Diuretics, which are routinely used for the relief of congestive symptoms and fluid retention.
- β-Blockers, to reverse ventricular remodelling.
- Aldesterone antagonists (e.g. spironolactone), for people resistant to other drug therapy.
- Digoxin – if symptoms continue despite ACE inhibitors, β-blocker and diuretic therapy, or if rate control is needed in patients with atrial fibrillation.
- Amiodarone, for ventricular arrhythmia.
- Anticoagulants, to reduce the risk of stroke.
- Aspirin, to reduce the risk of vascular events.
- Statins, to reduce the risk of myocardial infarction (MI) and stroke.
- Inotropic agents, to stimulate the heart muscle.
- Calcium channel blockers, for co-morbid hypertension and angina.

Invasive procedures with NICE Guideline recommendations[5]

- Coronary revascularisation: there is an absence of randomised controlled trial (RCT) data to support this procedure for HF.
- Cardiac transplantation: this is a possible option for people with severe refractory symptoms or refractory cardiogenic shock.
- Ventricular assist devices: there are insufficient data about the safety of these mechanical ventricular assist devices to recommend widespread use.
- Biventricular pacing: RCT data suggest that this should be considered for people with LVEF ≤35%, drug refractory symptoms and QRS >120 ms.
- Implantable cardioverter defibrillators (ICDs): recommendations for the use of these devices can be found in NICE Technology Appraisal Guidance No. 11: guidance on the use of implantable cardioverter defibrillators for arrhythmias (www.nice.org.uk/Docref.asp?d=10239).

In addition to the above, specialist heart nurse care and rehabilitation may be needed.

Relevant national guidelines, including National Service Frameworks, are as follows:

- NICE. MI. Secondary prevention (May 2007).
- NICE. Atrial fibrillation (June 2006).
- NICE. Implantable cardioverter defibrillators for arrhythmias (review). NICE; Report No. 11, 2005.
- NICE. Chronic heart failure. NICE; Report No. 5, 2003.
- NSF. Coronary heart disease: chapter 6, Heart failure. National Science Foundation, 2000.

Description of technology under assessment

Summary of intervention

Aim of cardiac resynchronisation therapy devices

The aim of cardiac resynchronisation therapy (CRT) devices is to improve the pumping

efficiency of the heart by (1) optimising atrioventricular delay and (2) reducing ventricular un-coordination to restore a more synchronous contraction pattern,[43] thereby reversing the remodelling of the left ventricle.

Cardiac resynchronisation therapy

This consists of inserting a pulse generator under the skin (usually) in the upper chest from which three leads pass transvenously into the heart. Leads are secured in the right atrium and the right ventricle, with the third directed to the left ventricle usually via the coronary sinus. This type of device is known as CRT-P. If an automatic ICD is included, the device is known as a CRT-D. After the atria contract, both ventricles are paced to contract at the same time. If the patient is in permanent atrial fibrillation, the atrial lead will be omitted.

Criteria for treatment

Criteria for the selection of suitable people for cardiac resynchronisation therapy are available in the clinical guidelines of NICE,[5,44] the ESC[42] and the US joint American College of Cardiology (ACC) and American Heart Association (AHA).[45,46] These are summarised in *Table 2* and also include, where relevant, the ICD criteria, given that some

TABLE 2 *Criteria for patient selection for CRT*

	CRT therapy	**ICD therapy**
NICE Guidelines[5,44] 2003 2006 ICDs	Drug refractory + NYHA class III–IV + EF <35% + QRS duration >120 ms	Primary prevention History MI >4 weeks + LVEF <35% or NVST on Holter + inducible VT on EPS History MI >4 weeks + LVEF <30% or QRS >120 ms Familial condition with risk of SCD Secondary prevention Sustained VT or VF Spontaneous sustained VT causing syncope or significant haemodynamic compromise Sustained VT without syncope or cardiac arrest + LVEF, <35% + NYHA III at worst
ESC Guidelines[42] 2005	CRT-P Drug refractory + NYHA class III–IV + QRS duration ⩾130 ms CRT-D Drug refractory + NYHA class III–IV + QRS duration ⩾130 ms	Primary prevention LVEF <30–35% Receiving optimal drug therapy >40 days post-MI Secondary prevention Sustained VT which is poorly tolerated or associated with reduced LVEF Survived cardiac arrest
ACA/AHA Guidelines[45,46] 2001 2005	Drug refractory + NYHA class III–IV + EF ⩽35% + QRS duration >120 ms	Primary prevention >40 days post-MI + LVEF <30% + NYHA class II-III + drug refractory Non-ischaemic cardiomyopathy + LVEF <30% + NYHA II-III + drug refractory Secondary prevention History of SCD History of VF Haemodynamically destabilising VF

EPS, electrophysiology study; NVST, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 3 *Service life expectancy of CRT devices*

Type of device	Range of life expectancy (years)	Source of information
CRT-P	3–6	Expert opinion
	5–8	Guidant, personal communication Expert opinion
CRT-D	3–5	Expert opinion
	4–7	Guidant, personal communication Expert opinion
ICD	5	Sanders *et al.*;[50] Medtronic, personal communication

people could receive a combined CRT and ICD device (CRT-D). Generally, guidelines recommend consideration of CRT for people with LVSD (LVEF ⩽35%), drug refractory symptoms and a QRS duration >120 ms. Only the ESC guidelines differentiate their recommendations for CRT-P and CRT-D devices, although they identify the same patient types as suitable for both devices.

Follow-up required

Following implantation of the device, optimisation of the pacemaker settings will be required.[47]

Technical difficulties

Implantation is technically more demanding than for other types of pacemaker due to the location of the third lead in a cardiac vein, which may have challenging anatomy. Furthermore, proximity to the left phrenic nerve and the resulting uncomfortable diaphragmatic stimulation during pacing limit the acceptability of pacing in some patents.[48] In addition, subsequent lead dislodgement occurs in up to 10% of initially successful implants, and further complications include cardiac perforation and coronary sinus dissection.[49]

Setting and equipment required

Devices may be implanted in district general hospitals or regional cardiac centres that have established facilities for pacemaker implantation. High-quality digital X-ray equipment is necessary for coronary sinus angiography and positioning of the left ventricular pacing electrode. Individuals who perform implantation will usually be senior cardiologists who have received specialist training in the technique, supported by cardiac technicians and nurses. Implanting centres should ideally be supported by at least two experienced implanters. Pacemaker optimisation during follow-up is essential; this requires support from senior cardiologists and technicians.

Currently, there are one to two suitably trained cardiologists in each regional centre and further training will provide a further cardiologist in each district general hospital (personal communication from clinical expert).

Service life of the pulse generator

The service life of the pulse generator of the CRT devices is variable, ranging from 4 to 8 years for a CRT-P and from 2 to 7 years for a CRT-D (*Table 3*).

Further considerations

Non-responders

Between 11 and 46% of people who receive a CRT device do not respond.[51] These are people who are successfully implanted with a device but fail to show an improvement in their condition. The technical definition of non-response and identification of non-responders is open to debate and is discussed in the section 'Identifying non-responder to CRT' (p. 32). The identification of these people is clearly important to the NHS.

Ischaemic versus non-ischaemic disease

A cohort study (N = 12,640 people) found that 36% of hospital admissions for HF had ischaemic heart disease.[52] It is important to know how people with ischaemic and non-ischaemic heart disease respond to CRT.

Atrial fibrillation

A population-based screening study (N = 3,960) found that 33% of those with HF also had atrial fibrillation (AF).[1] This may be an important subgroup as they have an increased likelihood of sudden death.[53] Many trials of CRT have excluded patients with AF (see the section 'Atrial fibrillation', p. 34).

Current usage in the NHS

The data on the number of people requiring CRT are both sparse and conflicting. McAlister and colleagues estimated that between 0.7% and 21% of people in Ontario presenting with LVSD were eligible for CRT, depending on whether the setting was a hospital or specialist clinic.[20] On

TABLE 4 *Purchase cost of CRT devices (in 2004 and 2005)*

System components	CRT-P		CRT-D	
	N	**Mean (£)**	***N***	**Mean (£)**
Whole system cost (device with leads)	192	3,809	239	16,001
Unit cost (pulse generator unit only)	177	2,687	157	14,391
Leads[a]	443	359[a]	443	359[a]

N, no. of patient procedures.
[a] Assumed that leads used by CRT-P and CRT-D devices are the same or sufficiently similar to not affect price. NB: Steroid-eluting leads appeared not to be priced very differently.
Source: Data supplied by NHS Purchasing and Supplies Agency (PASA) on prices paid by 61 NHS 'buying units' during 2004 and 2005. Only device models where more than 10 were purchased (across all buying units) were included in calculating this cost estimate.

average, these figures correspond to about six CRT implants per million.[54] A report from the European Heart Rhythm Association said that 1224 implants (504 CRT-P and 720 CRT-D devices) across 154 centres in England and Wales were carried out during 2004.[55] However, the rate of increase in implantation for both devices is about 50% per annum, which would give a figure of 2625 for 2005 (Central Cardiac Audit Database, personnel communication). These figures indicate that there were about 23 implants per million people in England and Wales.

Costs associated with intervention

In the chapter on economic modelling (Chapter 4) we produce comprehensive estimates of the cost implications of using CRT in patients with HF in the NHS. The average purchase costs of the devices themselves are given above, as sourced from the NHS Purchasing and Supplies Agency (*Table 4*). Data from the National Schedule of Reference Costs only show the total procedure cost for all types of pacemakers,[56] and current device list prices are typically higher than these figures.

Chapter 2

Definition of the decision problem

The decision problem

The intervention

Cardiac resynchronisation therapy

For the purpose of this report, the term cardiac resynchronisation therapy (CRT) is taken to be synonymous with the term biventricular pacing (BVP).

Population including subgroups

The population for this study is those people with HF (from any NYHA class) who have a marker of cardiac dyssynchrony (QRS duration >120 ms) and LVSD (LVEF ≤35%).

Subgroups of interest are:

- age
- AF
- NYHA class
- degree of LVSD, i.e. % LVEF
- degree of dyssynchrony
- ischaemic and non-ischaemic HF.

In addition, the role of ECHO in assessing LVSD is considered.

Relevant comparators

Relevant comparators are:

- optimal pharmaceutical therapy (OPT) alone
- or the alternative CRT device, i.e. CRT-P versus CRT-D.

Outcomes to be examined

The primary outcome of interest is mortality. This is examined in the following ways:

- progressive HF mortality
- non-HF mortality (including other cardiac mortality)
- all-cause mortality
- SCD.

Secondary outcomes of interest are:

1. The number of people who had HF hospitalisations.
2. Exercise capacity, measured by:
   (a) the 6-minute walk test
   (b) peak oxygen uptake
   (c) duration of exercise.
3. The number of people who experienced an adverse effect of treatment. An adverse event is defined as one that results in death or permanent disability or requires an invasive intervention to correct:
   (a) health-related QoL NYHA class before and after treatment
   (b) the MLWHF questionnaire[57]
   (c) EuroQol (EQ-5D): this is a generic preference-based QoL measure with five dimensions. Scores can range from 0 to 1, where 0 = death and 1 = full health; negative scores indicate a QoL considered to be worse than death.[58]

Key issues

- Clinical effectiveness.
- Cost-effectiveness.
- Adverse events.
- QoL.
- The effects of CRT in patients with AF.
- The effects of ischaemic and non-ischaemic heart disease on response to CRT.
- The role of ECHO in assessing LVSD and subsequent effects on the cost-effectiveness of interventions.

Overall aims and objectives of this assessment

The aim of this technology assessment review (TAR) is to assess the clinical and cost-effectiveness of CRT, with and without an ICD, for the treatment of HF (LVSD).

This aim is addressed through:

- a systematic review of clinical effectiveness literature about the technologies and possible meta-analysis
- a systematic review of published economic evaluations of the technologies
- an assessment of adverse events connected with the technology

- an examination of how the technology affects QoL
- the development of a decision analytic model to extend published results and to generate expected values for the health and cost gains/losses associated with each intervention.

The specific objectives of the report are:

- to evaluate the relative clinical effectiveness of CRT-P and CRT-D on overall survival, SCD, HF death, HF hospitalisation, QoL, exercise capacity and NYHA status compared with OPT or the alternative CRT device (CRT-P versus CRT-D)
- to evaluate the adverse events associated with CRT-P and CRT-D
- to estimate the incremental cost-effectiveness of CRT-P and CRT-D compared with OPT or the alternative CRT device (CRT-P versus CRT-D).

Areas outside this assessment

This assessment will not consider a comparison of CRT devices with stand-alone ICD devices. ICD devices have recently been the subject of NICE Guidelines.[59]

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

The clinical effectiveness of CRT was assessed by a systematic review of published research evidence. The review was undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[60]

Identification of studies

Search strategy

Electronic databases were searched for published systematic reviews and/or meta-analyses, RCTs and ongoing research in January 2006 and updated in June 2006. The updated search revealed no new systematic reviews or RCTs. Appendix 1 shows the databases searched and the strategies in full. Bibliographies of articles were also searched for further relevant studies, and the US Food and Drugs Administration (FDA) and European Regulatory Agency Medical Device Safety Service websites were searched for relevant material. No language restriction was applied to the search strategy.

Study identification

Relevant studies were identified in two stages. Abstracts returned by the search strategy were examined independently by two researchers (MF and RT) and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (MF and RT) examined these independently for inclusion or exclusion and disagreements were resolved by discussion. The process is illustrated by the QUOROM flow chart in Appendix 2.[61]

Inclusion and exclusion criteria

The inclusion criteria for studies of clinical effectiveness were as follows.

Study design

Included studies for clinical effectiveness had to be systematic reviews of RCTs or RCTs. Although we had considered relaxing these criteria for examining adverse events by including observational studies, such was the level of adverse event reporting in the RCTs in this review that this was deemed unnecessary.

Intervention

The intervention was either CRT-P or CRT-D.

Comparators

The comparators were:

- OPT alone
- or the alternative CRT device, CRT-P versus CRT-D.

Population

The population of interest is people with a diagnosis of HF due to LVSD, with evidence of cardiac dyssynchrony.

Data abstraction strategy

Data were independently extracted by two researchers (MF and RT). Disagreements were resolved by discussion. Actual numbers were extracted where possible. Such data are identified in the data extraction sheets. Data extraction forms for each included study are shown in Appendix 3.

Critical appraisal strategy

Assessments of RCT quality were performed using the indicators shown below. Results were tabulated and these aspects described.

Internal validity

1. Sample size:
   (a) power calculation at design.
2. Selection bias:
   (a) explicit eligibility criteria
   (b) proper randomisation and allocation concealment
   (c) similarity of groups at baseline.
3. Performance bias:
   (a) similarity of treatment other than the intervention across groups.
4. Attrition bias and intention-to-treat (ITT) analysis:
   (a) all patients are accounted for
   (b) number of withdrawals specified and reasons described
   (c) analysis undertaken on an ITT basis.
5. Detection bias:
   (a) blinding
   (b) objective outcome measures.
6. Appropriate data analysis.

Any potential conflict of interest was noted (for example, financial support provided to studies and/or authors by manufacturers of the devices).

External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Study findings can only be effectively generalisable if they (a) describe a cohort that is representative of the affected population at large or (b) present sufficient detail in their outcome data to allow the reader to extrapolate findings to a patient group with different characteristics.

Generalisability of included studies was assessed by examining the age, the percentage of participants with AF and the gender profile of the included patients, in addition to their baseline QRS and LVEF levels. Studies that appeared representative of the UK population with regard to these factors were judged to have high external validity.

Methods of analysis and synthesis

Details of the methods and results of included trials are tabulated and described in the text of this section. Dashes in the tables indicate that information was not reported.

Given the time-related nature of mortality and morbidity, where possible these outcomes were reported as hazard ratios (HRs) [with their 95% confidence intervals (CIs)]. Where not reported, HRs were derived from Kaplan–Meier curves or the log-rank test using the method of Parmar and colleagues.[62] The trials in this review reported outcomes at differing follow-up points. Pooling results at different time points depends on the assumption of a constant treatment effect over time. Using the outcome of time to all-cause death, we tested and confirmed the appropriateness of this assumption (see Appendix 5). Binary and continuous outcomes were summarised as relative risks and weighted mean differences, respectively. Given the potential for repeated events, hospitalisation related to HF was also expressed as a rate ratio. Risks of adverse events were combined using simple pooling, i.e. without weights and by study.

Where appropriate, data were pooled using a fixed-effects model, except where statistical heterogeneity existed ($p < 0.1$) according to the χ^2 statistic, when a random-effects model was used instead.[63–65] Reasons for heterogeneity were explored using meta-regression. Data are expressed as means and 95% CIs. All analyses were performed using Stata Software (Stata 8, StataCorp LP, College Station, TX, USA). Forest plots were produced using Stats Direct.

Five subgroups were identified at the outset. These were age, AF, NYHA class, degree of LVSD (i.e. % LVEF) and degree of dyssynchrony (i.e. QRS duration). The study reports of included trials were examined for data on these particular subgroups.

Potential publication bias was assessed by visual inspection of funnel plots and inferential testing using the Egger test.[63]

Results

A kappa test showed a good level of agreement between reviewers about which studies should be included in this review (kappa 0.81, 95% CI 0.74 to 0.88)

Quantity and quality of research available

Number of studies identified

We identified 18 systematic reviews and meta-analyses. Of these, five met the inclusion criteria.

There were 774 other studies identified, of which five met the inclusion criteria.

Details of the passage of studies through the selection process can be found in the flow chart in Appendix 2.

Number and type of studies included

Systematic reviews

Three systematic reviews plus meta-analyses, one systematic review and one meta-analysis were included in this TAR. These five studies were assessed against the QUOROM statement for assessing the criteria for the quality of reporting systematic reviews and meta-analyses.[61] Quality assessment forms are presented in Appendix 2.

- Freemantle and colleagues (2006).[66] This is a high-quality systematic review and meta-analysis of CRT against OPT, ICD and univentricular pacing. Eight RCTs were included, five of which are in this TAR. The other three studies had comparators that are outside the scope of this review.
- Pichon-Riviere and colleagues (2005).[67] This is an Argentinian systematic review of biventricular pacemakers. No quantitative synthesis was performed. Eight RCTs are included, four of

which are in this TAR; other studies had comparators and outcomes that are outside the scope of this review. Information about the criteria for selection, the date of the searches, the assessment of validity and data abstraction methods are limited.

- McAlister and colleagues (2004).[49] This is a high-quality systematic review and meta-analysis of CRT for congestive HF, with searches up to May 2004. Nine RCTs are included in the efficacy review and undergo meta-analysis. However, the scope for the McAlister review was broader than this TAR and includes studies of dual chamber and multi-site pacers as interventions and univentricular pacing and ICDs as controls, all of which are outside the remit for this report. Four of the five RCTs included in this TAR were included in the McAlister study, so it will be used as a source for data checking and for information about further studies from its bibliography.
- Bradley and colleagues (2003).[68] This is a high-quality systematic review and meta-analysis of CRT and death from progressive HF, with searches up to June 2002. Four RCTs were included, three of which are included in this TAR. The fourth study had a comparator outside the scope of this review (i.e. an ICD). This study was used for bibliographic information.
- Abdulla and colleagues (2006).[69] This recent high-quality systematic review and meta-analysis assessed RCTs and non-RCTs of CRT-P, CRT-D and ICD devices in people with HF, searching up to June 2005. Of the 10 studies included in this review, five are the same as those studies in this TAR, the additional studies being non-RCTs and RCTs with an ICD comparator, both of which are outside the scope of this report.

Randomised controlled trials

From the 81 RCTs of CRT, five trials (with 18 papers) were included in this report (see Appendix 3 for data extraction forms). Four of these trials had reported their findings in more than one paper; *Table 5* gives a summary of the included papers (information from FDA reports was also included).

Characteristics of the included studies

The characteristics of the studies are given in *Table 6*. Details of the studies are presented in Appendix 3. In all studies, all participants were given OPT.

CARE-HF[71] (*n* = 813), January 2001–March 2005

This parallel RCT had CRT-P as the intervention and OPT as the comparator. CARE-HF was a multi-centre trial (82) in 12 European countries, including the UK, of adults with heart failure in NYHA classes III–IV who had a QRS duration ⩾120 ms, an LVEF ⩽35% and who were in sinus rhythm. Participants were randomised prior to implantation and followed up initially for a mean of 29.4 months and then in an extension study for a mean of 36.4 months. The primary outcome measure was combined all-cause mortality and/or unplanned hospitalisation for HF. This trial was funded by Medtronic.

TABLE 5 *Included RCTs of cardiac resynchronisation therapy*

Trial	Included papers
CARE-HF	Cleland *et al.*, 2001,[70] 2005,[71] 2005,[72] 2004[73] + study update 2005[74]
COMPANION	Bristow *et al.*, 2000,[75] 2004[76] Carson *et al.*, 2005[77] FDA report[78]
CONTAK-CD	Phase I Saxon *et al.*, 1999[79] Lozano *et al.*, 2000[80] Phase I & II Higgins *et al.*, 2003[81] Knight *et al.*, 2004[82] FDA report 2002[83]
MIRACLE	Abraham *et al.*, 2001,[84] 2002[6] Aranda *et al.*, 2004[85] Leon *et al.*, 2005[86] Woo *et al.*, 2005[87] FDA report 2001[88]
MUSTIC-SR	Cazeau *et al.*, 2001[89]

COMPANION[76] (*n* = 1520), January 2000–December 2002

This parallel RCT had CRT-P or CRT-D as the intervention and OPT as the comparator. COMPANION was a multi-centre trial (128) in the USA of adults with HF in NYHA classes III–IV who had a QRS ⩾120 ms and an LVEF ⩽35%. Participants were randomised before implantation and followed up for a mean time of 14.6 months. The primary outcome measure was combined all-cause mortality and all-cause hospitalisation. This study was stopped early after 1638 patients were enrolled after predictions that the primary and secondary mortality end-points had been met. This trial was funded by Guidant.

CONTAK-CD[81] (*n* = 581), February 1998–December 2000

Data from both phases of this RCT have been included. Participants were recruited as one cohort at the time of implantation and allocated to one of

two phases. Phase I (n = 222) was a randomised crossover trial and Phase II was a parallel RCT (n = 279). 'CRT-D: on' was the intervention and 'CRT-D: off' was the control [CRT was inhibited, VVI 40 , but defibrillating capacity was available (background inactive pacing was provided in CONTAK-CD, MIRACLE and MUSTIC-SR; in CONTAK-CD and MUSTIC-SR this was VVI 40, in which the ventricle pacing is inactive at 40 beats per minute)]. CONTAK-CD was a multi-centre trial (47) in the USA, Europe and Australia of people with HF in NYHA classes II–IV who had a QRS ⩾120 ms and an LVEF ⩽35%. People with AF were excluded. Additionally, participants were required to have VT as an indication for an ICD. Participants were randomised 30 days after they were implanted and followed up for 6 months. The primary outcome measure was progressive HF mortality in Phase I and a composite of all-cause mortality, hospitalisation for worsening HF and ventricular tachyarrhythmia (VT) needing device therapy in Phase II. This trial was funded by Guidant.

MIRACLE[6] (n = 453), November 1998–December 2000

This parallel RCT had 'CRT-P: on' as the intervention and 'CRT-P: off' as the comparator [CRT was inhibited, virtual device interface (VDI)]. (In MIRACLE this was set to VDI, where the ventricle is paced, atrium and ventricle are sensed but there is no response to the sensing.) MIRACLE was a multi-centre trial[6] in the USA and Canada of people with HF in NYHA classes II–IV who had a QRS ⩾130 ms and an LVEF ⩽35%. People who had an episode of AF within the last month were excluded. Participants were randomised after they were implanted and followed up for 6 months. This study had three primary outcome measures: NYHA class, MLWHF score and the distance walked in 6 minutes. This trial was funded by Medtronic.

MUSTIC-SR[89] (n = 67), March 1998–March 1999

This randomised controlled cross-over trial had 'CRT-P: on' as the intervention and 'CRT-P: off' as the comparator (CRT was inhibited, VVI 40). MUSTIC-SR was a multi-centre trial[89] in Europe of people with HF in NYHA class III who had a QRS ⩾150 ms and an LVEF ⩽35%. People who had an episode of AF within the last month were excluded. Participants were randomised 2 weeks postimplant and followed up for 6 months. The primary outcome measure was the distance walked in 6 minutes. This trial was funded by Medtronic and Sorin.

Studies of device compared CRT implanted with no implant and studies of mode compared CRT implanted (device turned on) with CRT implanted (device turned off).

Number and type of studies excluded

Of the 18 systematic reviews and meta-analyses identified, two did not concern CRT and 11 were actually non-systematic narrative reviews. These were excluded at the abstract stage.

Of the 81 RCTs of CRT, 58 of these were excluded at the abstract stage. Appendix 2 gives the reasons for exclusion. Of the remaining 23 RCTs, five papers were excluded: two papers were of subgroup analyses outside the scope of this TAR, one had inappropriate outcomes, one only had postcrossover data and in one the pre-/postcrossover data could not be separated out. Appendix 4 gives a table of excluded studies with rationale.

Methodological quality

The included studies were assessed for internal and external validity. The quality of included studies is summarised in *Table 7*.

For clarity of presentation, the following citations should be assumed to be the references for the included trials unless stated otherwise:

- CARE-HF: Cleland and colleagues[71,74]
- COMPANION: Bristow and colleagues[76]
- CONTAK-CD: Higgins and colleagues[81]
- MIRACLE: Abraham and colleagues[6]
- MUSTIC-SR: Cazeau and colleagues.[89]

Internal validity

Similarity of groups at baseline

All studies reported that intervention and control groups were similar at baseline. However, there were differences between the studies in when baseline measures were taken. In CARE-HF, baseline measures were taken prior to randomisation and implant; in COMPANION, randomisation was prior to implant but baseline measures were taken 1 week postimplant; in CONTAK-CD, baseline measures were taken prior to implant and 30 days prior to randomisation; in MIRACLE, baseline measures were taken before implant and randomisation; and in MUSTIC-SR, baseline measures were taken postrandomisation and 2 weeks postimplant (*Table 8*).

These variations in baseline measurement in relation to randomisation and implantation may have affected the comparability of the outcomes.

TABLE 6 *Study characteristics*

Parameter	CARE-HF	COMPANION	CONTAK-CD	MIRACLE	MUSTIC-SR
Study design	Parallel RCT	Parallel RCT	Phase I randomised crossover trial Phase II parallel RCT	Parallel RCT	Cross-over RCT
Sample size	813	1520	581	453	67
Intervention	CRT-P on	CRT-P or CRT-D	CRT-D on	CRT-P on	CRT-P on
Comparator	OPT	OPT	CRT-D off VVI 40 [ventricle inhibited (inactive) pacing at a basic rate of 40 bpm]	CRT-P off VDI (ventricle paced, A and V sensed, no response to sensing)	CRT-P off VVI 40 [ventricle inhibited (inactive) pacing at a basic rate of 40 bpm]
Concurrent treatment	OPT	OPT	OPT	OPT	OPT
Setting	Multiple (82)	Multiple (128)	Multiple (47)	Multiple (44)	Multiple (15)
No. of centres	12 European countries	USA	Phase I USA, Europe and Australia Phase II USA	USA and Canada	Europe
Length of follow-up (months)	Main study mean 29.4 Extension study mean 36.4	Data were collected at 3-month intervals postrandomisation Median duration of primary end point: CRT-P 16.2 CRT-D 15.7 OPT 11.9	6 months	6 months	6 months
NYHA	III–IV	III–IV	II–IV	III–IV	III
Primary outcome measure	Progressive HF mortality	All-cause mortality and all-cause hospitalisation	Progressive HF mortality All-cause mortality, hospitalisation for worsening HF and VT needing device therapy	NYHA class MLHFQ 6-minute walk	6-minute walk distance
Was ECHO used for entry criteria?	Yes to assess dyssynchrony (if <150 ms) and to optimise the timing of CRT	Not mentioned	Yes to assess dyssynchrony	Not mentioned	Yes to determine optimal atrioventricular delay
How were people assigned to NYHA class?	The worst status in the preceding week	Not mentioned	Not mentioned	Not mentioned	Not mentioned
No. of leads	3	3	3	3	3
AV node ablation	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Right bundle branch block %	Not mentioned	2	13	9	Not mentioned
Study inclusion criteria in addition to those of this TAR	Age ≥18 years	Age ≥18 years	Age ≥18 years	Age ≥18 years	HF for ≥3 months
	HF symptoms >6 weeks	LVEDD ≤60 mm		HF for >1 month	LVEDD ≥60 mm

continued

TABLE 6 *Study characteristics (cont'd)*

Parameter	CARE-HF	COMPANION	CONTAK-CD	MIRACLE	MUSTIC-SR
Study exclusion criteria in addition to those of this TAR	LVEDD ⩾30 mm	PR interval >150 ms	Indication for ICD	LVEDD ⩾55 mm	Sinus rhythm
	Sinus rhythm Contraindications for pacemaker[a] or ICD Major CV event in previous 6 weeks Life expectancy <1 year On IV treatment for HF Persistent AF or atrial flutter Cardiac surgery or other major events ⩽6 weeks Tricuspid prosthesis	ICD indications Bradycardia stimulation MI within 60 days of randomisation Life expectancy <6 months Indications for anti-bradycardia pacing Chronic atrial tachyarrhythmias Unexplained syncope Uncontrolled blood pressure Surgically uncorrected primary valvular heart disease Progressive or unstable angina Hypertrophic obstructive cardiomyopathy Amyloid disease Tricuspid prosthesis Hospitalisation for HF >4 hours in previous month	Currently have ICDs/candidates for ICD therapy Indications for permanent pacing Life expectancy <6 months History of AF Indication for anti-bradycardia pacing History of VT/VF Chronic drug-refractory atrial tachyarrhythmias	QRS interval ⩾130 ms Presence of pacemaker or ICD Indication for or contraindication to cardiac pacing Unstable angina, acute MI, coronary surgery ⩽3 months Cardiac or cerebral ischaemic event ⩽3 months Life expectancy <6 months AF ⩽1 month Severe primary pulmonary disease 6-minute walk ⩾450 m	QRS interval ⩾150 ms An indication for an ICD Hypertrophic or restrictive cardiomyopathy Suspected acute myocarditis Life expectancy <1 year Cardiac or cerebral ischaemic event within previous 3 months or had AF within previous month Revascularisation in previous 3 months or scheduled Tachycardia Treatment-resistant hypertension An inability to walk Obstructive lung disease Reduced life expectancy not associated with CVD ACS lasting ⩽3 months Correctable vulvopathy

ACS, acute coronary syndromes; AV, aventricular, CV, cardiovascular, IV, intravenous; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire.
[a] Conventional pacemaker.

TABLE 7 *Summary of quality criteria for included RCTs*

Criterion	CARE-HF	COMPANION	CONTAK-CD	MIRACLE	MUSTIC-SR
Power calculation	Yes	Yes	No	Yes	Yes
Randomisation method	Unknown but minimisation used Stratified by NYHA class	Unknown Stratified by β-blockers and NYHA class	Unknown but block randomisation used	Unknown but block randomisation used	Unknown but block randomisation used Stratified by centre
Allocation concealment	Yes – fax to central office	Unknown	Unknown	Yes – sealed envelope	Unknown
Assessors blinded	No	No	Double blinded, but who is not known	Yes, both patients and assessors	Not known if patients were blinded
Groups similar at baseline	Yes	Unknown	Yes	Yes	Yes
ITT	Yes	Yes	No	Yes	Yes
Protocol violations specified	Yes Crossovers noted	No	No	Yes Crossovers before 6 months	Yes Crossovers before 3 months
Missing value treatment	No loss to follow-up or missing data reported	People who withdrew and who had no primary outcome data were regarded as censored	Unknown	Last value carried forward in analysis	No imputation for missing cases undertaken
Attrition	Withdrawals with reasons were given	Withdrawals were specified but no reasons given	Withdrawals with reasons were given in some cases	Withdrawals with reasons were given	Withdrawals with reasons were given
All patients accounted for?	Yes	Yes	No	Yes	Yes
Randomisation after implantation?	No	No	Yes – 30 days postimplant	Yes – interval not stated	Yes – 2 weeks postimplant
When were baseline measures taken?	At randomisation	1 week postimplant	At implant and at randomisation	7 days before implantation	4 weeks before implant and at randomisation

TABLE 8 *Order of events in taking baseline measures*

Study	Study type	Event 1	Event 2	Event 3
CARE-HF	Device	Randomisation	Baseline	Implant
COMPANION	Device	Randomisation	Implant	Baseline
CONTAK-CD	Mode	Baseline	Implant	Randomisation
MIRACLE	Mode	Baseline	Implant	Randomisation
MUSTIC-SR	Mode	Implant	Randomisation	Baseline

Outcome measures from studies that allowed a recovery period postimplant are likely to show a better response and fewer adverse events than those that did not. Studies that randomised people postimplant will have selected only those patients who survived and did well.

Sample size

Four of the included trials (CARE-HF, COMPANION, MIRACLE and MUSTIC-SR) included power calculation statements that the trials were powered to detect a difference in their primary outcome measure. However, CONTAK-

CD was not sufficiently powered to detect a significant difference in the primary outcome measure as the event rate was only half of that expected.

Selection bias
None of the included trials described their method of generating random allocation.

CONTAK-CD, MIRACLE and MUSTIC-SR used block randomisation, whereas CARE-HF used minimisation techniques. COMPANION, did not report on randomisation methods but did report stratification for β-blockers. CARE-HF and COMPANION stratified for NYHA class and MUSTIC-SR stratified by centre; MIRACLE did not use stratification.

Two of the trials, CARE-HF, and MIRACLE, reported that allocation to groups had been concealed. COMPANION, CONTAK-CD and MUSTIC-SR did not report on this matter.

Both CARE-HF and COMPANION did not employ any form of blinding. MUSTIC-SR blinded their participants to allocation group and CONTAK-CD and MIRACLE stated that they used double blinding. Lack of blinding may introduce important biases, particularly for subjective outcomes.[90,91]

Performance bias
In all the trials, participants in the intervention and control groups appeared to be treated equally apart from CRT.

Detection bias
The MIRACLE and CONTAK-CD studies reported that assessors were blinded; the other studies did not comment on this matter.

Attrition bias and intention-to-treat analysis
With the exception of CONTAK-CD, all participants in the trials were accounted for. In the control arm of CARE-HF, 43 (11%) people had a CRT-P device and 23 (6%) had a CRT-D device implanted and activated. In COMPANION, 120 (39%) of those in the control group withdrew (primarily due to crossovers to the intervention groups), whereas 103 (17%) of those in the intervention arms withdrew. In CONTAK-CD, 14 (2%) of those enrolled withdrew. In the MIRACLE study, seven people withdrew (1.5%) and there were 10 crossovers. MUSTIC-SR reported four withdrawals (6%) and one crossover. In all trials, withdrawals were specified and, except for COMPANION, reasons were clearly described. All trials followed up intervention and control groups in the same way.

Only MIRACLE and MUSTIC-SR specified protocol violations; in both cases these were crossovers before the specified time. As the analyses were conducted as ITT, this could have the effect of reducing the difference between control and intervention outcomes.

All the trials used ITT analysis, with the exception of CONTAK-CD, where participants were analysed according to the treatment they had received except for operative mortality.

Other issues
In the COMPANION trial, the definition of hospitalisation changed three times during the study. These changes increased the length and scope of the meaning of hospitalisation. Furthermore, people who had prolonged implantation/re-implantation stays, due to adverse events, did not have these episodes included as hospitalisations.[92]

Another issue about the internal validity of the COMPANION trial centres on the withdrawal of participants from the control arm of the study who were in need of CRT implantation to avoid being counted as crossovers. This strategy undermines the ITT analysis of the study as these participants should have continued to be included in the control group analyses. The authors were advised by the FDA to re-consent these withdrawn participants and reassess their outcomes.[93]

External validity

Populations

Age. The mean age of the populations of the trials was similar, ranging from 63 to 67 years. This is younger than the mean age of those first admitted to hospital with HF in Scotland (74 years), which is assumed to be similar to England and Wales.[52]

QRS. The included trials' participants had a QRS duration ranging between ⩾120 and ⩾150 ms.

LVEF. All the trials included people with an LVEF ⩽35%.

NYHA. The trials included people with an NYHA classification of functional ability ranging from II to IV, which is representative of the range of symptomatic HF, although only one trial included class II (CONTAK-CD).

Settings
The trials were conducted in multiple settings around the world including the UK (CARE-HF $n = 147$). The expertise of the surgical team is only commented on in CARE-HF, where participants were operated on either in an expert centre or with the assistance of an expert implanter. It is assumed that the other trials used experienced clinicians to deliver the intervention to maximise the outcomes. This being the case, the trial outcomes may underestimate the complication rate and overestimate the benefits in real-world practice.

Treatment variables
In all trials, participants received comparable devices and OPT.

Outcome variables
The types of outcomes were similar in all trials, although there was variation in the primary outcome measure. All trials considered mortality and functional outcomes appropriate to people with HF.

Summary
Although a number of issues have been raised about the internal and external validity of the included trials, we believe that they are generally of good quality and that the issues identified are unlikely to have substantially biased the results or to have had a substantial impact on generalisability.

Assessment of effectiveness and synthesis of information
The main outcomes considered were:

- mortality (all-cause, cardiac-related, sudden death and non-cardiac death)
- morbidity (HF hospitalisations, worsening HF and arrhythmias)
- NYHA class
- exercise capacity
- health-related QoL
- adverse effects (CRT and non-CRT related events).

Three comparisons are presented:

- CRT-P versus optimal medical therapy
- CRT-D versus optimal medical therapy
- CRT-P versus CRT-D.

Results are reported by outcome (number of patient events). These include results reported in publications other than the main trial reports (e.g. FDA documents) and also subgroup analyses. In addition to tabulation of the results from the literature, pooled estimates were calculated and presented in Forest plots. Unless indicated otherwise, results are based on ITT analyses.

Mortality
All-cause mortality
All trials provided data on all-cause mortality (*Table 9* and *Figure 2*). When CRT-P trials were combined (MUSTIC-SR, MIRACLE, COMPANION and CARE-HF), there was an HR of 0.68 (95% CI 0.54 to 0.88, $p = 0.001$) for CRT-P compared with OPT. The pooled HR (CONTAK-CD and COMPANION) for all-cause death with CRT-D compared with OPT was 0.65 (95% CI 0.49 to 0.85, $p < 0.0001$). There was no evidence of significant heterogeneity (CRT-P, $Q = 4.09$, $p = 0.252$; CRT-D, $Q = 0.034$, $p = 0.853$). Direct comparison of CRT-D and CRT-P in COMPANION showed no difference in the risk of overall mortality [relative risk (RR) 1.20, 95% CI 0.96 to 1.51, $p = 0.115$]. However, this estimate should be treated with caution, as this trial was not powered to compare the two devices directly. Meta-regression analysis (using an indirect comparison of outcomes between studies, i.e. comparison of CRT-P and CRT-D studies where the common comparator is OPT), confirmed that there was no evidence of significant difference between the two device types (HR 1.10, 95% CI 0.78 to 1.53, $p = 0.290$). Excluding the small MUSTIC-SR trial, the annual risk of all-cause death ranged across trials from 14 to 20%. There was little evidence of heterogeneity in the effect of CRT across follow-up times ($Q = 5.292$, $p = 0.259$); Appendix 5.

Heart failure death
Deaths due to HF were only reported by COMPANION and CARE-HF (*Table 10*, *Figure 3*). A reduction in progressive HF death with CRT-P was seen in the combined trial data (pooled HR 0.62, 95% CI 0.46 to 0.83, $p < 0.0001$), but in COMPANION for CRT-D (HR 0.73, 95% CI 0.47 to 1.11, $p = 0.143$) this was not significant. There was no evidence of heterogeneity for CRT-P ($Q = 0.727$, $p = 0.394$). There were insufficient data to undertake meta-regression analysis.

Cardiac death
Only the COMPANION trial reported total cardiac deaths. The risks of cardiac death at 12 months' follow-up in patients in the OPT, CRT-P and CRT-D arms were 17.5, 17.1 and 12.8%, respectively. Compared with OPT there was reduction in cardiac events with CRT-D ($p = 0.006$) but not in the case of CRT-P ($p = 0.334$).

TABLE 9 *All-cause mortality*

Study	Follow-up (months)	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
MUSTIC-SR	6 (%)	3/29 (10)	0/29 (0)	RR: 7.00[a]	0.38 to 129.70, $p = 0.191$[a]
MIRACLE	6 (%)	12/228 (5.3)	16/225 (7.1)	HR: 0.73	0.34 to 1.54, $p = 0.40$
COMPANION	16.2 vs 11.9[b] (%)	131/617 (21)	77/308 (25)	HR: 0.76	0.58 to 1.01, $p = 0.059$
	29.4[b] (%)	82/409 (20.0)	120/404 (29.7)	HR: 0.64	0.48 to 0.85, $p < 0.002$
CARE-HF	36.4	101/409 (24.7)	154/404 (37.4)	HR: 0.60	0.47 to 0.77, $p < 0.0001$
		CRT-D: *n*/*N* (%)	**OPT: *n*/*N* (%)**		
CONTAK-CD	3 or 6	11/245	16/245	RR: 0.69[a]	0.33 to 1.45, $p = 0.326$[a]
COMPANION	15.7 vs 11.9[b] (%)	105/595 (18)	77/308 (25)	HR: 0.64	0.48 to 0.86, $p = 0.003$
		CRT-P: *n*/*N* (%)	**CRT-D: *n*/*N* (%)**		
COMPANION	16.2 vs 15.7[b] (%)	131/617 (21)	105/595 (18)	RR: 1.20[a]	0.96 to 1.51, $p = 0.115$[a]

[a] Calculated by the authors of this report.
[b] Mean follow-up duration.

TABLE 10 *Heart failure death*

Study	Follow-up (months)	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
COMPANION	16.2 vs 11.9[b] (%)	53/617 (8.6)	34/308 (11.0)	HR: 0.71	0.46 to 1.09, $p = 0.112$
CARE-HF	29.4[b]	33/409 (8.8)	56/404 (13.8)	RR: 0.58[a]	0.39 to 0.87, $p = 0.009$[a]
	36.4[b]	38/409 (9.3)	64/404 (15.8)	HR: 0.55	0.37 to 0.82, $P = 0.003$
		CRT-D: *n*/*N* (%)	**OPT: *n*/*N* (%)**		
COMPANION	15.7 vs 11.9[b] (%)	52/595 (8.7)	34/308 (11.0)	HR: 0.73	0.47 to 1.11, $p = 0.143$
		CRT-P: *n*/*N* (%)	**CRT-D: *n*/*N* (%)**		
COMPANION	16.2 vs 15.7[b] (%)	53/617 (8.6)	52/595 (8.7)	RR: 0.98[a]	0.68 to 1.42, $p = 0.926$[a]

[a] Calculated by the authors of this report.
[b] Mean follow-up duration.

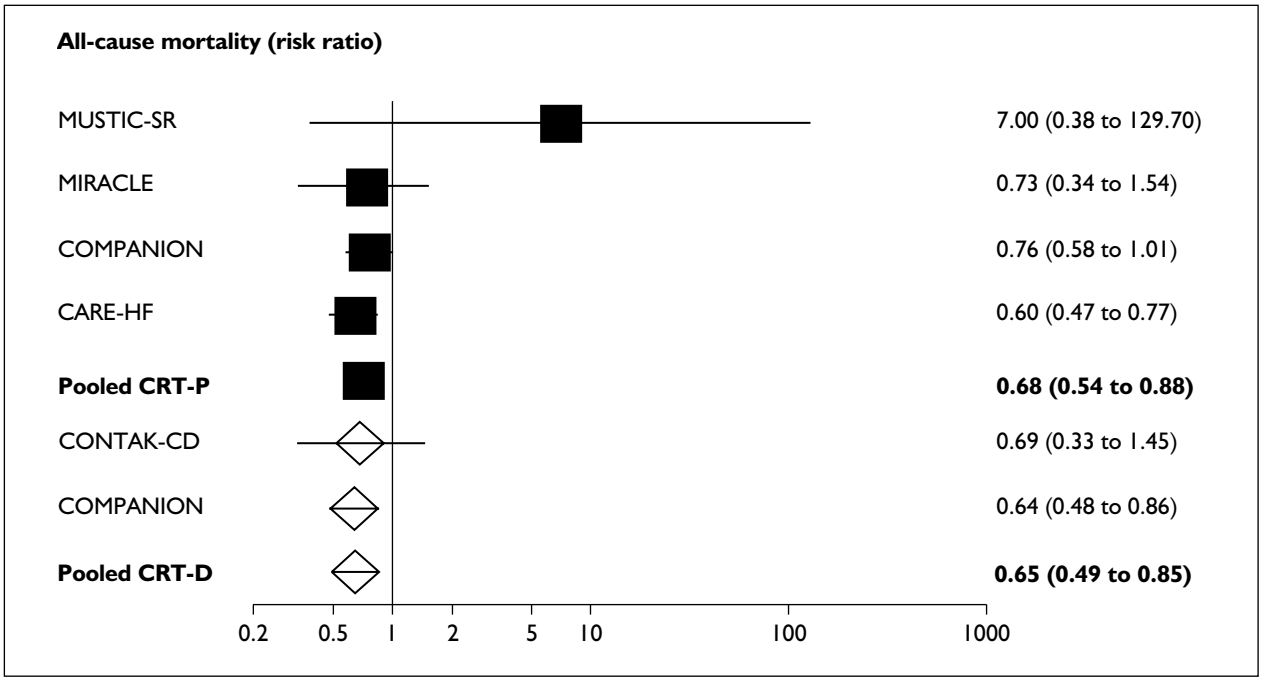

FIGURE 2 *Forest plot of all-cause mortality versus OPT*

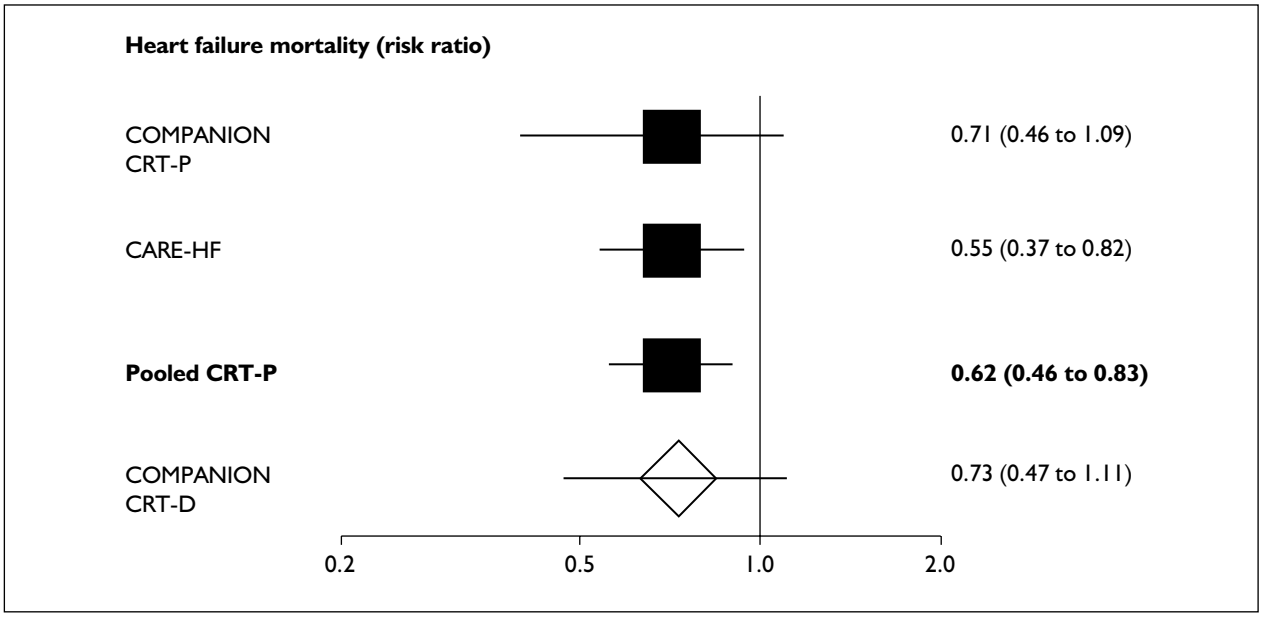

FIGURE 3 *Forest plot of heart failure death versus OPT*

Sudden cardiac death

SCD was reported by MIRACLE (FDA report), MUSTIC-SR, COMPANION and CARE-HF trials (*Table 11*, *Figure 4*). There was evidence of heterogeneity in the effect of CRT-P on the risk of SCD across trials ($Q = 6.689$, $p = 0.035$). CARE-HF reported a reduction in SCD at both 29.4 and 36.4 months with CRT-P. However, COMPANION reported a higher risk of SCD with CRT-P (7.8%) than OPT (5.8%) ($p = 0.485$). Based on a random effects model, the pooled HR across trials (MUSTIC-SR, COMPANION and CARE-HF) for CRT-P was 0.75 (95% CI 0.45 to 1.18, $p = 0.198$). In contrast, the COMPANION trial shows there was a reduction in SCD with CRT-D compared with OPT (HR 0.44, 95% CI 0.23 to 0.86, $p = 0.02$). The risk of SCD in patients receiving a CRT-P device (7.8%) was higher than in patients who received a CRT-D device (2.9%) ($p < 0.0001$). Meta-regression analysis provides some evidence

TABLE 11 *Sudden cardiac death*

Study	Follow-up (months)	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
MUSTIC-SR	6 (%)	2/29 (6.9)	0/29 (0)	RR: 5.00[a]	0.25 to 99.18, $p = 0.292$[a]
COMPANION	16.2 vs 11.9[b] (%)	48/617 (7.8)	18/308 (5.8)	HR: 1.21	0.70 to 2.07, $p = 0.485$
CARE-HF	29.4[b]	29/409 (7.0)	38/404 (9.4)	RR: 0.75[a]	0.47 to 1.19, $p = 0.232$[a]
	36.4[b]	32/409 (7.8)	54/404 (13.4)	HR: 0.54	0.35 to 0.84
MIRACLE	6	7/228 (3.1)	5/225 (2.2)	RR: 1.38[a]	0.44 to 4.28, $p = 0.578$[a]
		CRT-D: *n*/*N* (%)	**OPT: *n*/*N* (%)**		
COMPANION	15.7 vs 11.9[b] (%)	17/595 (2.9)	18/308 (5.8)	HR: 0.44	0.23 to 0.86, $p = 0.02$
		CRT-P: *n*/*N* (%)	**CRT-D: *n*/*N* (%)**		
COMPANION	16.2 vs 15.7[b] (%)	48/617 (7.8)	17/595 (2.9)	RR: 2.72[a]	1.58 to 4.68, $p < 0.0001$[a]

[a] Calculated by the authors of this report.
[b] Mean follow-up duration.

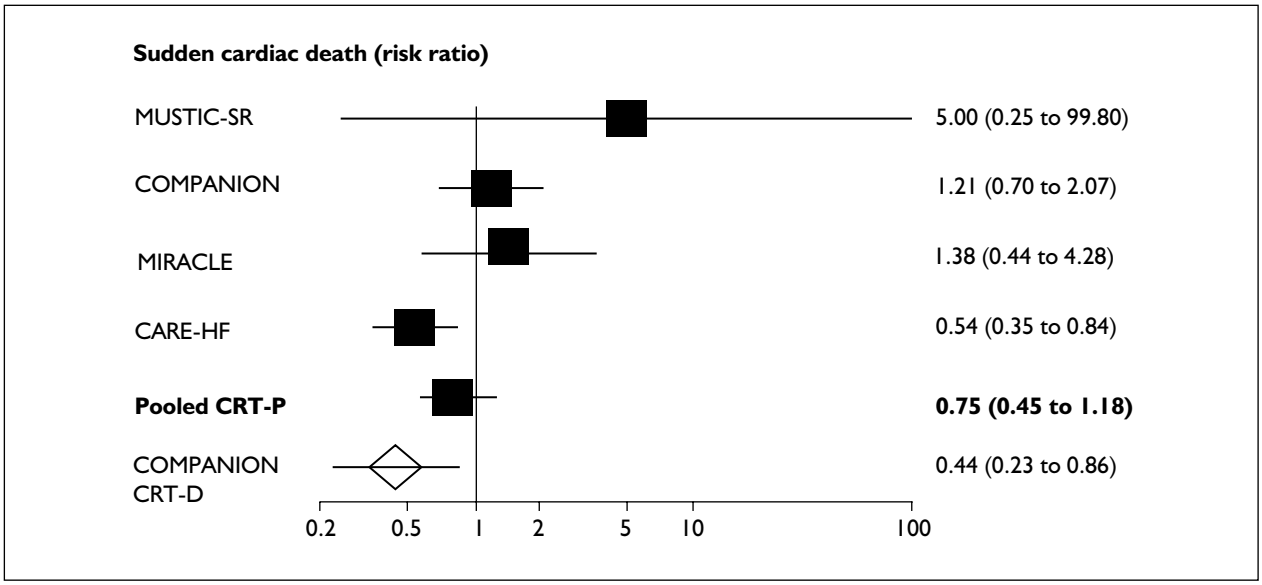

FIGURE 4 *Forest plot of sudden cardiac death*

of a trend towards a larger treatment effect for CRT-D compared with CRT-P, although this difference was not statistically significant (HR 2.02, 95% CI 0.49 to 8.78, $p = 0.345$). Excluding the small MUSTIC-SR trial, the annual risk of SCD in OPT-treated patients across the trials ranged from 3.8 to 4.6%.

Other causes of death

An analysis of causes of death in patients in the OPT, CRT-P and CRT-D arms of the COMPANION trial showed no evidence of important differences in vascular death (0 vs 0.8 vs 0.5%), non-cardiac death (3.6 vs 2.3 vs 3.5%) or unknown causes of death (2.6 vs 0.5 vs 0.8%) at follow-up. Other trials did not provide information on non-cardiac deaths.

Morbidity

Three indices of morbidity were reported by the included trials: hospitalisation due to HF, worsening HF and arrhythmias.

Hospitalisations related to heart failure

Although all trials reported hospitalisation related to HF, it was defined in differing ways (*Tables 12* and *13*, *Figure 5*). Furthermore, the FDA report of COMPANION reported hospitalisation for HF or cardiovascular disease only as an event rate.

Numbers of people who were hospitalised due to heart failure

There was consistent and marked reduction in the number of people who had HF hospitalisations across trials with CRT-P (pooled HR 0.48, 95% CI 0.37 to 0.61, $p < 0.0001$). There was no evidence of heterogeneity in CRT-P effect across trials ($Q = 0.385$, $p = 0.825$). Although CONTAK-CD showed some reduction in HF rehospitalisation at 3 or 6 months, this trend was not significant (RR 0.82, 95% CI 0.52 to 1.26). Meta-regression analysis (indirect comparison) showed no evidence of significant difference between the two device types (HR 1.43, 95% CI 0.65 to 3.13, $p = 0.369$).

Number of events of hospitalisations

To allow comparison, the number of events was expressed as an event rate per 100 person years: no. of events × [100/follow-up (years) × no. of patients]. There was a significant reduction in the rate of HF hospitalisation with both CRT-P (pooled rate ratio 0.56, 95% CI 0.48 to 0.66, $p < 0.0001$) and CRT-D (rate ratio 0.59, 95% CI 0.49 to 0.70, $p < 0.0001$). Although the rate of hospitalisation in OPT patients varied across trials, there was no evidence of significant heterogeneity in CRT effect (CRT-P, $Q = 20.348$, $p = 0.555$). The COMPANION trial did not report the number of hospitalisations in the CRT-P arm, therefore it is not possible to compare CRT-P and CRT-D directly.

Worsening heart failure

Worsening HF (or decompensation) was reported by MUSTIC-SR, MIRACLE and CARE-HF, although, again, its definition varied across trials (*Table 14*, *Figure 6*). The risk of worsening HF was consistently reduced with CRT-P (pooled HR 0.67, 95% CI 0.46 to 0.84, $p = 0.026$). There was no significant heterogeneity ($Q = 2.57$, $p = 0.276$). No trial data for this outcome were available for CRT-D.

TABLE 12 *Hospitalisation related to heart failure: patient risk*

Study	Outcome, follow-up	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
MUSTIC-SR	Hospital admission because of decompensated HF, 3 months (%)	3/29 (10.3)	9/29 (31.0)	RR: 0.33[a]	0.10 to 1.10, $p = 0.07$[a]
MIRACLE	Hospitalisation for heart failure, 6 months (%)	18/228 (7.8)	34/225 (15.1)	HR: 0.50	0.28 to 0.88, $p = 0.02$
CARE-HF	Unplanned hospitalisation with worsening HF, 29.4 months[b] (%)	72/409 (17.6)	133/404 (32.9)	HR: 0.48	0.36 to 0.64, $p < 0.0001$
		CRT-D: *n*/*N* (%)	**OPT: *n*/*N* (%)**		
CONTAK-CD	HF hospitalisation, 3 or 6 months (%)	32/245 (13.1)	39/245 (15.9)	RR: 0.82[a]	0.52 to 1.26, $p = 0.326$[a]

[a] Calculated by the authors of this report.
[b] Mean follow-up duration.

TABLE 13 *Hospitalisation related to heart failure: per event*

Study	Outcome, follow-up	CRT-P: events per 100 patient years	OPT: events per 100 patient years	Rate ratio	95% CI, *p*-value
MIRACLE	Hospitalisation for heart failure, 6 months (%)	21.92	44.44	0.49[a]	0.31 to 0.80, $p = 0.004$[a]
COMPANION	Hospitalisation for heart failure, NR vs 12.1 months[b]	NR	69.43[a]	–	–
CARE-HF	Unplanned hospitalisation with worsening HF, 29.4 months[b] (%)	22.15[a]	38.75[a]	0.57[a]	0.48 to 0.67, $p < 0.0001$[a]
		CRT-D: events per 100 patient years	**OPT: events per 100 patient years**		
COMPANION	Hospitalisation for HF, NR vs 12.1 months[b] (%)	40.51	69.43[a]	0.59[a]	0.49 to 0.70, $p < 0.0001$[a]
		CRT-P: events per 100 patient years	**CRT-D: events per 100 patient years**		
COMPANION	Hospitalisation for HF, NR vs 12.1 months[b] (%)	NR	40. 1	–	–

NR, not reported.
[a] Calculated by the authors of this report.
[b] Mean follow-up duration.

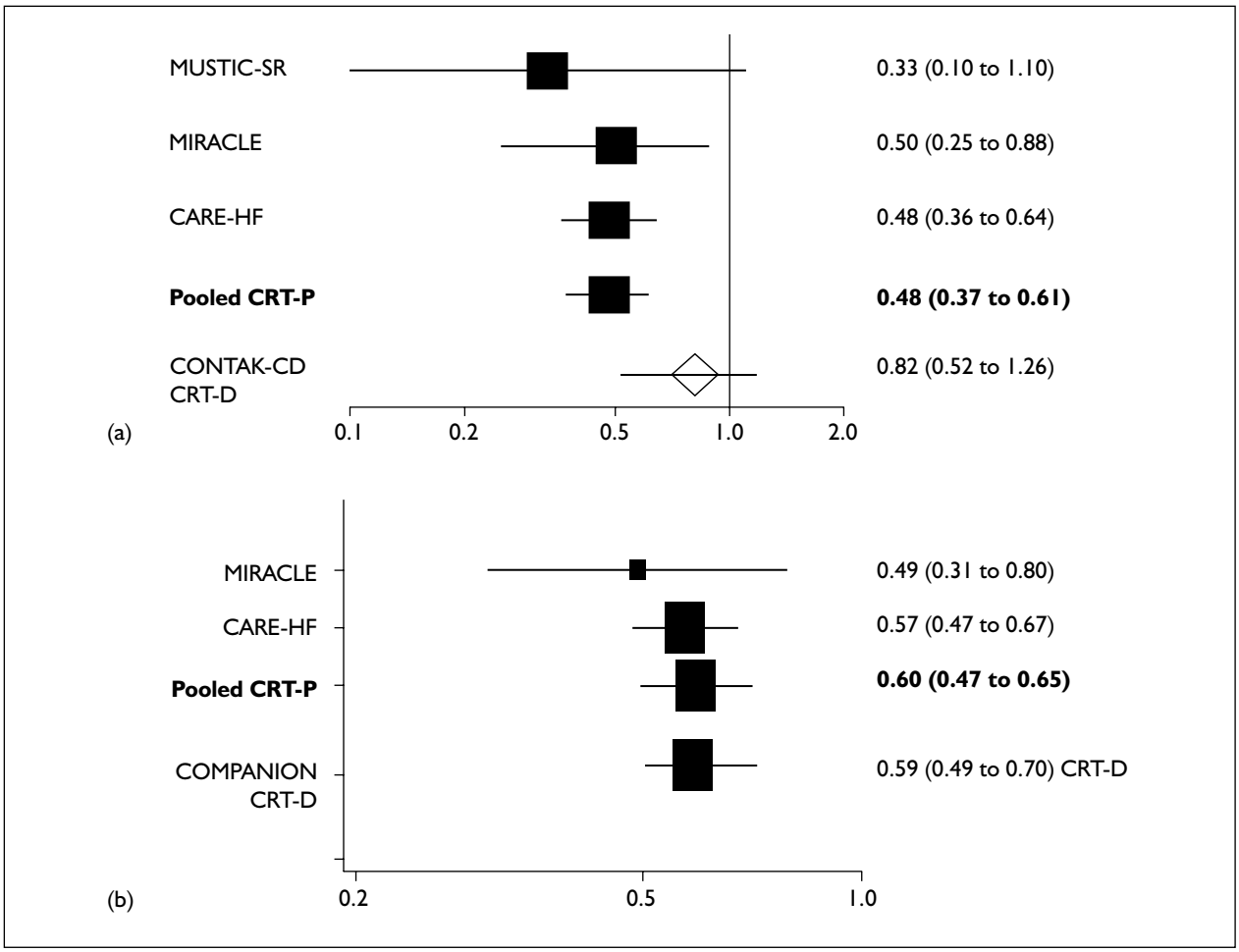

FIGURE 5 *Forest plots of hospitalisation due to heart failure: (a) risk ratio and (b) rate ratio*

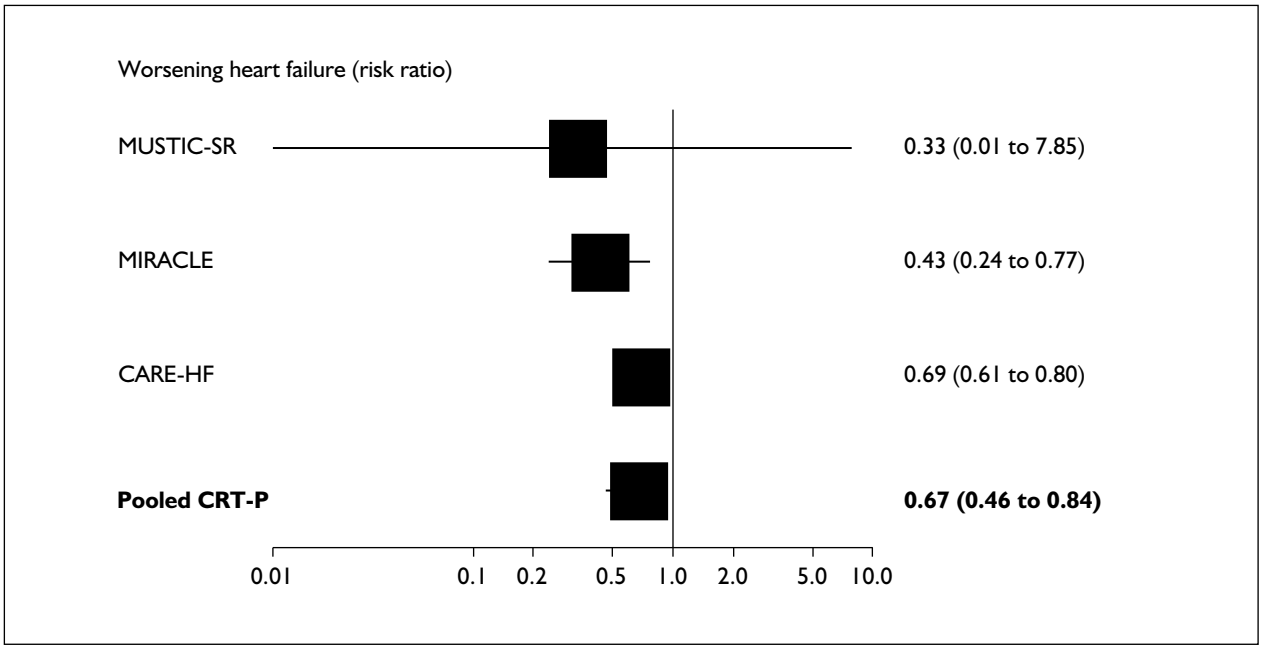

FIGURE 6 *Forest plot of worsening heart failure*

TABLE 14 *Worsening heart failure*

Study	Outcome, follow-up	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
MUSTIC-SR	Severe decompensation, 3 months (%)	0/29 (0)	1/29 (3.4)	RR: 0.33[a]	0.01 to 7.85, $p = 0.496$[a]
MIRACLE	Heart failure requiring i.v. medication, 6 months (%)	16/228 (7.0)	35/225 (15.6)	HR: 0.43	0.24 to 0.77, $p = 0.004$
CARE-HF	Worsening HF, 29.4 months[b] (%)	191/409 (46.7)	263/405 (64.9)	RR: 0.69[a]	0.61 to 0.80[a], $p < 0.001$

[a] Calculated by the authors of this report.
[b] Mean follow-up duration.

TABLE 15 *Arrhythmias*

Study	Outcome, follow-up	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
MUSTIC-SR	AF, 6 months (%)	0/29 (0)	1/29 (3.4)	RR: 0.33[a,b]	0.01 to 7.85, $p = 0.496$[a]
CARE-HF	Atrial arrhythmias or ectopy, 29.4 months[b] (%)	64/409 (15.6)	41/405 (10.1)	RR: 1.54[a]	1.07 to 2.23, $p = 0.020$[a]
		CRT-D: *n*/*N* (%)	**OPT: *n*/*N* (%)**		
CONTAK-CD	VT, 6 months (%)	36/245 (15.0) [221][c 94]	39/245 (16%) [139][c 94]	RR: 0.92[a]	0.61 to 1.41, $p = 0.707$

[a] Calculated by the authors of this report.
[b] Correction for zero cells applied.
[c] [ ], Number of events.

Arrhythmias

MUSTIC-SR and CARE-HF reported differing measures of atrial arrhythmias in both CRT and OPT groups. The FDA reports for CONTAK-CD and MIRACLE provided details on the number of ventricular tachycardias (*Table 15*). Given the difference in measures, pooling was deemed inappropriate. Compared with OPT, there was no evidence of a consistent effect of CRT-P on atrial arrhythmias.

NYHA class

All trials reported the change in NYHA functional class at follow-up (*Table 16*). There was a consistent increase in patients experiencing an improvement in one or more NYHA classes with both CRT-P (pooled RR 1.69, 95% CI 1.51 to 1.88, $p < 0.0001$) and CRT-D (pooled RR 1.52, 95% CI 1.28 to 1.82, $p < 0.0001$), compared with OPT (CRT-P versus OPT: CARE-HF, COMPANION, MIRACLE and MUSTIC-SR; CRT-D versus OPT: COMPANION and CONTAK-CD). There was no evidence of significant heterogeneity (CRT-P, $Q = 0.59$, $p = 0.746$; CRT-D, $Q = 0.81$, $p = 0.369$). The results of the COMPANION trial suggest that this improvement in NYHA class appears to occur within the first 3 months of CRT implantation.

Direct comparison in COMPANION of CRT-D versus CRT-P showed no significant difference in treatment effect (RR 1.07, 95% CI 0.96 to 1.19, $p = 0.202$) and HR. Indirect comparison showed CRT-P to have somewhat larger treatment effect than CRT-D (RR 1.32, 95% CI 1.03 to 1.70, $p = 0.027$).

Exercise capacity

All trials assessed exercise capacity (at 3–6 months' follow-up), with the exception of CARE-HF (*Table 17*). Exercise capacity was reported either as absolute values at follow-up or as the change from baseline to follow-up. As we are interested in between-group differences, both sets of results were pooled (it was assumed that the baseline values were equal). Significant improvements were seen with CRT-P in 6-minute walk distance (pooled mean difference +35.3 m, 95% CI +20.0 to +50.7, $p < 0.0001$), total exercise time (mean difference +62 s, 95% CI +25 to +99, $p < 0.0001$) and peak oxygen uptake (pooled mean difference +0.91 ml/kg/min, 95% CI +0.9 to +1.82, $p = 0.030$). Improvements were also seen for CRT-D in 6-minute distance (pooled mean difference +30.1 m, 95% CI +14.9 to +45.1, $p < 0.0001$) and total exercise time (mean difference +62.0 m, 95% CI +24.9 to +99.1, $p = 0.001$). There was no evidence of significant heterogeneity for CRT-P ($Q = 1.43$, $p = 0.489$) or CRT-D ($Q = 2.52$, $p = 0.111$) versus OPT. In direct comparison, there was no significant difference in 6-minute walk distance between CRT-P and CRT-D (mean difference –6 m, 95% CI –19.9 to +7.0, $p = 0.397$). This was confirmed by meta-regression (mean difference –5.3, 95% CI –31.9 to 20.4, $p = 0.685$).

Quality of life

Heath-related QoL was assessed at 3–6 months' follow up using the MLWHF scale[57] in all trials (*Table 18*). MLWHF scores were reported either as absolute values at follow-up or as the change from baseline to follow-up. Again, both were pooled. Improvements in MLWHF were seen with both CRT-P (pooled mean difference –9.9, 95% CI –12.2 to –7.6, $p < 0.0001$) and CRT-D (pooled mean difference –13.1, 95% CI –16.8 to –9.3, $p < 0.0001$). The CARE-HF trial also reported a significant improvement at 90 days in EQ-5D, a generic measure of QoL (mean difference +0.08, 95% CI +0.04 to +0.12, $p < 0.001$). No difference was seen in MLWHF in the direct comparison of CRT-P and CRT-D from COMPANION, or meta-regression (mean difference –3.5, 95% CI –7.6 to 1.2).

Subgroup analyses

Subgroup analyses were reported by CARE-HF, COMPANION, CONTAK-CD and MIRACLE (*Table 19*).

Subgroup effects were examined in CONTAK-CD, COMPANION and CARE-HF using appropriate statistical methods (i.e. treatment–subgroup interaction or heterogeneity test) (*Table 20*).[95] As MIRACLE presented analyses stratified by subgroup with no mention of an interaction test (or equivalent), their findings are not discussed here. Only the authors of CARE-HF stated that they defined their subgroups in advance. No trial reported a significant subgroup effect for outcomes (either composite or single). However, this finding should be interpreted with some caution, as the trials were not powered to detect such subgroup effects. Interestingly, CRT had less effect on functional outcomes (QoL, exercise capacity and NYHA class at follow-up) in the 32% patients in NYHA class II than the remaining group of patients in class III or IV. However, only one trial had NYHA class II data (CONTAK-CD).

Ischaemic heart failure

Given the data available, it was possible to use univariate meta-regression to explore potential subgroup effects of type of HF (ischaemic versus non-ischaemic) and NYHA class, mean age, mean

TABLE 16 *NYHA class*

Study	Outcome, follow-up	CRT-P: *n*/*N* (%)	OPT: *n*/*N* (%)	Effect	95% CI, *p*-value
MIRACLE	Improved ⩾1 class, 6 months	143/211 (67.8)	74/196 (37.8)	RR: 1.79[a]	1.47 to 2.20, $p < 0.0001$[a]
COMPANION	Improved ⩾1 class, 3 months	320/551 (58)	58/242 (24)	RR: 2.42[a]	1.91 to 3.07[a], $p < 0.001$
	Improved ⩾1 class, 6 months	298/489 (61)	76/199 (38)	RR: 1.59[a]	1.32 to 1.93[a], $p < 0.001$
CARE-HF	Improved ⩾1 class, 18 months	255/409 (62.3)	151/405 (37.2)	RR: 1.67[a]	1.44 to 1.94, $p < 0.0001$
	Mean class (SD), 90 days	2.7 (0.9)	2.1 (1.0)	MD: 0.6	0.4 to 0.7, $p < 0.001$
		CRT-D: *n*/*N* (%)	**OPT: *n*/*N* (%)**		
CONTAK-CD	Improved ⩾1 class, 30 days	39/109 (35.8)	37/116 (31.8)	RR: 1.12[a]	0.78 to 1.62, $p = 0.538$[a]
COMPANION	Improved ⩾1 class, 3 months	299/543 (55)	58/242 (24)	RR: 2.30[a]	1.81 to 2.91, $p < 0.0001$[a]
	Improved ⩾1 class, 6 months	283/497 (57)	76/199 (38)	RR: 1.49[a]	1.23 to 1.81, $p < 0.001$[a]
		CRT-P: *n*/*N* (%)	**CRT-D: *n*/*N* (%)**		
COMPANION	Improved ⩾1 class, 3 months	320/551(58)	299/543 (55)	RR: 1.05[a]	0.95 to 1.17, $p = 0.315$[a]
	Improved ⩾1 class, 6 months	298/489 (61)	283/497 (57)	RR: 1.07[a]	0.96 to 1.19, $p = 0.202$[a]

MD, mean difference; SD, standard deviation.
[a] Calculated by the authors of this report.

TABLE 17 *Exercise capacity*

Study	Outcome, follow-up	CRT-P	OPT	Effect: MD	*p*-Value
MUSTIC-SR	6-minute walk (m) at 3 months' follow-up	*N* = 22; mean 384.1 (SD 78.9)	*N* = 24; mean 316.2 (SD 141.8)	NR	$p < 0.001$
	Peak O_2 uptake (ml/kg/min), 3 months	*N* = 18; mean 15.9 (SD 5.8)	*N* = 20; mean 14.8 (SD 3.9)	NR	$p = 0.03$
MIRACLE	Change in 6-minute walk (m), 6 months	*N* = 214; median +39 (95% CI +26 to +54)	*N* = 198; median +10 (95% CI 0 to +25)	NR	$p = 0.005$
	Change in peak O_2 uptake (ml/kg/min), 6 months	*N* = 158; median +1.1 (95% CI –0.6 to 1.7)	*N* = 145; median +0.2 (95% CI –0.2 to +0.8)	NR	$p = 0.009$
	Change in total exercise time (s)	*N* = 159; median +81 (95% CI +62 to +119)	*N* = 146; median +19 (95% CI –1 to +47)	NR	$p = 0.001$
COMPANION	Change in 6-minute walk (m), 3 months	*N* = 422; mean 33 (SD 99)	*N* = 170; mean 9 (SD 84)	NR	$p < 0.001$
	Change in 6-minute walk (m), 6 months	*N* = 373; mean 40 (SD: 96)	*N* = 142; mean 1 (SD 93)	NR	$p < 0.001$
CONTAK-CD	Change in 6-minute walk (m), 3 or 6 months	*N* = 224; mean 35 (SD 105)	*N* = 220; mean 15 (SD 104)	NR	$p = 0.043$
	Change in peak O_2 uptake (ml/kg/min), 3–6 months	*N* = 216; mean 0.8 (SD 11.8)	*N* = 201; mean 0.0 (SD 5.7)	NR	$p = 0.030$
COMPANION	Change in 6-minute walk (m), 3 months	*N* = 420; mean 44 (SD 109)	*N* = 170; mean 9 (SD 84)	NR	$p < 0.001$
	Change in 6-minute walk (m), 6 months	*N* = 378; mean 46 (SD 98)	*N* = 142; mean 1 (SD 93)	NR	$p < 0.001$
		CRT-P	**CRT-D**		
COMPANION	Change in 6-minute walk (m), 3-months	*N* = 422; mean 33 (SD 99)	*N* = 420; mean 44 (SD 109)	NR	NR
	Change in 6-minute walk (m), 6-months	*N* = 373; mean 40 (SD 96)	*N* = 378; mean 46 (SD 98)	NR	NR

MD, mean difference; NR, not reported; SD, standard deviation.

TABLE 18 *Health-related quality of life*

Study	Outcome, follow-up	CRT-P	OPT	Effect: MD	95% CI, *p*-value
MUSTIC-SR	MLWHF score, 3 months	*N* = 23; mean 33.2 (SD 22)	*N* = 22; mean 44.0 (SD 25)	NR	$p < 0.001$
MIRACLE	Change in MLWHF score, 6 months	*N* = 213; median –18 (95% CI –22 to –12)	*N* = 193; median –9 (95% CI –12 to –5)	NR	$p = 0.001$
COMPANION	Change in MLWHF score, 3 months	*N* = 510; mean –24 (SD 27)	*N* = 243; mean –9 (SD 21)	NR	$p < 0.001$
	Change in MLWHF score, 6 months	*N* = 460; mean –25 (SD 26)	*N* = 207; mean –12 (SD 23)	NR	$p < 0.001$
CARE-HF	MLWHF score, 90 days	*N* = 409; mean 31 (SD 22)	*N* = 404; mean 40 (SD 22)	Mean –10	–8 to –12, $p < 0.001$
	EQ-5D score, 90 days	*N* = 409; mean 0.70 (SD 0.28)	*N* = 404; mean 0.63 (SD 0.29)	Mean 0.08	0.04 to 0.12, $p < 0.001$
		CRT-D	**OPT**		
CONTAK-CD	Change in MLWHF score, 3–6 months	*N* = 234; mean –7 (SD 30.5)	*N* = 225; mean +5 (SD 30)	NR	$p = 0.390$
COMPANION	Change in MLWHF score, 3 months	*N* = 514; mean –24 (SD 28)	*N* = 243; mean –9 (SD 21)	NR	$p < 0.001$
	Change in MLWHF score, 6 months	*N* = 478; mean –26 (SD 28)	*N* = 207; mean –12 (SD 23)	NR	$p < 0.001$
		CRT-P	**CRT-D**		
COMPANION	Change in MLWHF score, 3 months	*N* = 510; mean –24 (SD 27)	*N* = 514; mean –24 (SD 28)	NR	NR
	Change in MLWHF score, 6 months	*N* = 460; mean –25 (SD 26)	*N* = 478; mean –26 (SD 28)	NR	NR

TABLE 19 *Subgroup analyses conducted by the trials*

CARE-HF	COMPANION	CONTAK-CD	MIRACLE
Age, sex, NYHA, dilated cardiomyopathy, SBP, NT-BNP, LVEF, ESVI QRS, IMD, GFR, medication	Ischaemic heart failure, age, sex, NYHA class, LVDD, medication	β-Blockers, ischaemic HF, LVEF, left or right bundle branch block, QRS, sex, age	β-Blockers, ischaemic HF, LVEF, left or right bundle branch block, QRS, sex, age

ESVI, end-systolic volume index; GFR, glomerular filtration rate; IMD, Index of Multiple Deprivation; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; NT-BNP, plasma N-terminal brain natriuretic peptide.

TABLE 20 *Subgroup analyses*

Study	Method	Subgroups	Outcome(s) assessed	Statistically significant subgroup effects ($p \leq 0.05$)
CONTAK-CD	*Post hoc* specification Interaction term	NYHA class (I/II vs III/IV); QRS interval; morphology (LBBB vs NSIVCD) Aetiology (ischaemic vs non-ischaemic) LVEF	Primary outcome – composite (all-cause mortality, HF hospitalisation or ventricular tachyarrhythmias requiring device therapy) Secondary outcomes – peak VO_2; 6-minute walk; HRQoL; NYHA class at follow-up	NYHA + VO_2 NYHA + HRQoL NYHA + 6-minute walk NYHA + NYHA class at follow-up LBBB/NSIVCD + VO_2 LVEF + VO_2
COMPANION	Not stated if *pre* or *post hoc* Stratified analysis and interaction term	Age; sex; aetiology (ischaemic vs non ischaemic); NYHA class (III vs IV); LVEF; LVEDD; QRS interval; morphology (LBBB vs other); heart rate; SBP; diastolic BP; drug (ACE, β-blocker, loop diuretic, spinolacetone)	Primary outcome – composite (all-cause mortality or hospitalisation for any cause); all-cause mortality	None reported
CARE-HF	*Pre hoc* specification Stratified comparison and heterogeneity test	Age; sex; NYHA class (III vs IV); LVEF; dilated cardiomyopathy; NT-BNP; ESVI; QRS interval; morphology (LBBB vs other); SBP; GFR; drug (ACE, β-blocker, loop diuretic, spinolacetone, digoxin)	Primary outcome (composite: all-cause mortality or HF hospitalisation)	None reported

ESVI, end-systolic volume index; GFR, glomerular filtration rate; HRQoL, health-related quality of life; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NSIVCD, no specific intraventricular conduction delay; NT-BNP, plasma N-terminal brain natriuretic peptide; SBP, systolic blood pressure; VO_2, oxygen uptake.

QRS duration and mean LVEF at baseline across trials (*Table 21*). There was no evidence of significant univariate subgroup effects. However, these analyses need to be interpreted with considerable caution, as they are based on aggregate level data from a small number of fairly homogeneous trials.

Left and right bundle-branch block

Not all studies reported the numbers of participants who had left or right bundle-branch block (LBBB/RBBB) or outcomes by this measure. Of the studies that reported this (COMPANION, CONTAK-CD, MIRACLE and MUSTIC-SR), the incidence was from 14% in COMPANION, 57% in CONTAK-CD and 87% in MUSTIC-SR. Details are given in Appendix 3.

Adverse events

The published reports of trials included in this review did not consistently report adverse events. Additional information was sought from FDA reports (for COMPANION, CONTAK-CD, MIRACLE and MUSTIC-SR). The focus of reporting was events and complications in patients receiving CRT. *Table 22* reports the perioperative and postoperative risks from individual studies and the pooled results. This was generally reported as ≤7 days and ≤8 days from implant. These results should be treated with caution as the

TABLE 21 *Univariate meta-regression subgroup analyses:* p-*values*

Outcome subgroup	All-cause mortality	HF hospitalisation	6-minute walk	MLWHF
Ischaemic HF (%)	0.699	0.393	0.081	0.171
NYHA class IV (%)	0.828	0.318	0.134	0.239
NYHA class II (%)	0.991	0.369	0.127	0.645
Mean age (years)	0.955	0.873	0.911	0.661
Mean QRS duration (mm)	0.325	0.496	0.433	0.600
Mean LVEF (%)	0.995	0.571	0.563	0.127

trials varied in how events were classified, particularly with regard to whether they were peri- or postoperative.

The procedure used to implant a CRT device is complicated and a significant minority of operations performed end in failure.[86] From the studies included in this TAR, the combined population of 2823 attempted implants resulted in 265 failures (9.4%).

There were 21 perioperative deaths in 2757 patients (pooled risk 0.8%, 95% CI 0.5 to 1.2%). CRT device implants were successful on average in 90.8% (95% CI 89.6 to 92.0%) of patients; there was no clear evidence of a difference in implanting success between CRT-P and CRT-D devices (*Table 23*). Where details were given, implant failures were due to problems with the left ventricle lead. The most frequent postoperative event was lead dislodgement (7.9%, 95% CI 6.4 to 9.7%). Peri- and postoperative risk appeared to be consistent across trials and CRT devices. COMPANION reported a risk of moderate to severe adverse events of 10% (62/617) for CRT-P and 8% (48/595) for CRT-D ($p = 0.42$).

COMPANION reported a slightly higher overall risk of moderate to severe adverse events for any cause with CRT (OPT, 188/595, 61%; CRT-P, 407/617, 65%; CRT-D, 410/595, 69%). There were no significant differences in risk of respiratory tract infection, hypotension, falls or syncope, acute coronary syndromes, ventricular arrhythmias and neurological events between CRT and control groups in CARE-HF.

Publication bias

There was no evidence of significant funnel plot asymmetry across the principle outcomes reported [i.e. all-cause mortality ($p = 0.206$), HF hospitalisation ($p = 0.873$), 6-minute walk ($p = 0.174$) and MLWHF ($p = 0.412$)]. However, given the small number of trials included, the power of the Egger test is likely to be low. See Appendix 5 for funnel plots.

Identifying non-responders to CRT

Between 11 and 46% of people who receive a CRT device do not respond,[96] as determined by clinical and ECHO parameters, usually measured at 3 and 6 months. Whereas clinical parameters may be subjective, ECHO parameters are less so and can be used to establish the degree of improvement in function by measuring left ventricular volumes and EF. ECHO response has been defined in a number of ways,[96] including as a decrease of >15% in left ventricular end-systolic volume (LVESV) and clinical response as an improvement of ⩾1 NYHA class.[97] Subjective or functional outcomes suggest a lower non-response rate (11–26%) than objective remodelling ones (40–46%); these differences have been explained by the placebo effect of device implantation.[51] However, it is possible for people to show a response using ECHO but not clinically, and vice versa.[97]

Echocardiography – role in assessing LVSD

The important role of ECHO in assessing LVSD was highlighted in the Chapter 2. LVSD is a key marker of HF. Once it has occurred, the heart responds through remodelling. ECHO may allow further identification of potential responders to CRT, based on assessment of inter- and intraventricular dyssynchrony, that is, LVSD. Breithardt and colleagues' study indicates the usefulness of ECHO in identifying potential responders to CRT through identifying those with significant delay in lateral wall motion.[98] Bax and colleagues concluded that ECHO is the most practical approach to evaluate dyssynchrony and predict response to CRT.[99]

A number of ECHO techniques can be used to make this assessment, including

- M-mode ECHO
- two-dimensional ECHO
- tissue Doppler imaging (TDI).

Summary

It seems likely that mechanical rather than electrical dyssynchrony may predict suitability for

TABLE 22 *Adverse events with CRT*

	MUSTIC-SR	MIRACLE	CONTAK-CD	COMPANION[a]	CARE-HF	Total *n*/*N* (%; 95% CI)
Perioperative period: *n*/*N* (%)						
Lead-related	–	32/528 (6)	8/109 (7)	CRT-P 62/617 (10) CRT-D 48/595 (8)	24/409 (5.8)	174/2258 (7.7; 6.7 to 8.8)
Device-related	–	1/528 (0.2)	–	–	14/409 (3)	15/937 (1.6; 1.0 to 2.6)
Infection	–	–	–	–	3/409 (0.7)	3/409 (0.7; 5.8 to 9.1)
Surgical complication	–	39/571 (7)	–	–	10/409 (2)	49/980 (5)
Postoperative period: *n*/*N* (%)						
Device-related	2/58 (3.4)	13/528 [13] (2.4)	–	–	–	15/586 (2.6; 1.6 to 4.2)
Lead-related	8/58 (13.8)	45/528 [54] (8.5)	29/448[a] [29] (6.5)	–	–	82/1034 (7.9; 6.4 to 9.7)
Infection	–	7/528 [7] (1.3)	7/448[a] [7] (1.6)	–	–	14/976 (1.4; 1.2 to 3.0)
Surgical complication	–	6/528 (1)	–	–	–	–
All complications[b]	10/58 (17.2)	[c]	[c]	110/1212 (9.0) CRT-P: 62/617 (10) CRT-D: 48/595 (8)	51/409 (12.5)	377/2655 (14.2; 12.9 to 15.6)
Peri- and postoperative period: *n*/*N* (%)						
Deaths	0/64	2/571 (0.3)	10/501 (1.9)	8/1212 (0.7) CRT-P: 5/617 (0.8) CRT-D: 3/595 (0.5)	1/409 (0.2)	21/2757 (0.8; 0.5 to 1.2)
Implant failures	5/64 (7.8)	43/571 (7.5)	66/567 (11.6)	132/1212 (10.8) CRT-P 78/617 (13) CRT-D 54/595 (9)	19/409 (4.6)	265/2823 (9.4; 8.3 to 10.5)

n, no. of people; [*n*], number of events; *N*, total number of people.
[a] From COMPANION trial data.
[b] Total events that include lead infection, lead-related events, lead perforation and dissections, device-related and surgical related events.
[c] All complication data for MIRACLE and CONTAK-CD have not been reported as the peri- and postoperative data had different denominators.

TABLE 23 *Percentage of successful implant procedures in each trial*

CARE-HF	COMPANION	CONTAK-CD	MIRACLE	MUSTIC-SR
95	87	88	93	92

Source: Freemantle and colleagues, 2006.[66]

CRT. This indicates that ECHO, which measures mechanical dyssynchrony, rather than ECG, which measures electrical dyssynchrony, is likely to be more useful in assessing suitability for CRT. However, none of the major trials of CRT used ECHO measures of dyssynchrony as the principal criteria for assessing eligibility.

This technology has cost implications for the NHS, as the national average unit cost of ECHO is £59 whereas that of 12-lead ECG is £25.[56]

Atrial fibrillation

None of the trials in this TAR included patients with AF. A small number of studies (fewer than 200 people) have shown that CRT may improve functional capacity (e.g. 6-minute walk) and haemodynamic markers in these people.[100–105] In most cases, ablation of the atrio-ventricular node was performed before CRT implantation.

Of the studies excluded from this TAR, four reported on AF.[101–104] Only two of these studies (MUSTIC AF and Garrigue and colleagues) concerned people with HF. MUSTIC AF compared CRT-P with right ventricular pacing and showed no significant effects.[101] Garrigue and colleagues also showed no significant difference in the 6-minute walk test but did show a statistically significant improvement in a haemodynamic marker.[103]

Summary

The role of CRT in people with heart failure and atrial fibrillation remains uncertain.

Summary of clinical effectiveness

1. Five RCTs (3434 participants) met the inclusion criteria for the review. All were described as randomised.
2. Although there were some concerns about the internal and external validity of the trials, mainly due to inadequate reporting, overall they were of moderate to good quality.
3. CRT devices reduce mortality and hospital admissions and improve health related QoL in NYHA class III or IV HF, for people receiving optimal pharmaceutical therapy with low EF ($\leqslant$35%) and dyssynchrony (QRS interval >120 ms).
4. There is currently limited direct evidence comparing CRT-P and CRT-D devices. However, the effects of the two devices on patient-related outcomes appear to be equivalent, with the exception of an additional reduction in SCD with CRT-D.
5. There was no clear evidence to support a differential effect of CRT in a particular subgroup of people, although this conclusion should be treated with caution given the limited power for such analyses. The trials excluded patients with AF or an indication for an ICD.
6. Serious events due to CRT devices appear to be infrequent, at least up to 2 years postimplant (14% overall complications and 0.8% deaths). Complications that are reported include lead displacement, infection and mechanical dysfunction. A proportion (9%) of CRT implantations were unsuccessful.

Chapter 4

Assessment of cost-effectiveness

Systematic review of economic evaluations of CRT

Aim

The aim of this chapter is to summarise existing published research evidence on the costs and cost-effectiveness of CRT compared with OPT, with particular emphasis on the potential generalisability of previous studies to the NHS policy and clinical context.

Methods

Search strategy

Appendix 1 describes the sources searched and the search strategy for MEDLINE. No language restriction was applied to the search strategy.

Study selection criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations were identical with those for the systematic review of clinical effectiveness, except that:

- Non-randomised studies were included (including, for example, decision model-based analyses or analyses of patient-level cost and effectiveness data alongside observational studies).
- Only full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequence analyses were included (economic evaluations which only report average cost-effectiveness ratios were included only if the incremental ratios could easily be calculated from the published data).
- Stand-alone cost analyses based in the UK NHS were also sought.

Based on the above inclusion/exclusion criteria, study selection was made by one reviewer (RA).

Study quality assessment

The methodological quality of the economic evaluations was assessed according to the international consensus-developed criteria list of questions developed by Evers and colleagues.[106] Any studies based on decision models were also assessed against the ISPOR guidelines for good practice in decision analytic modelling.[107]

Data extraction strategy

Data were extracted by one researcher (RA) into two summary tables, one to describe the study design of each economic evaluation and the other to describe the main results (see Appendix 6).

In the study design table, author and year; model type or trial based; study design [e.g. cost-effectiveness analysis (CEA), cost–utility analysis (CUA) or cost analysis]; service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features were recorded (see *Table 79* in Appendix 6).

For modelling-based economic evaluations, a supplementary study design table recorded further descriptions of: model structure [noting its consistency with the study perspective, and knowledge of disease/treatment processes; sources of transition and chance node probabilities; sources of utility values; sources of resource use and unit costs; handling of heterogeneity in populations; evidence of validation (e.g. debugging), calibration against external data and comparison with other models].

In the results table, for each comparator we show incremental cost, incremental effectiveness/utility and incremental cost-effectiveness ratios (ICERs). Excluded comparators on the basis of dominance or extended dominance were also noted. The original authors' conclusions were noted, and also any issues that they raised concerning the generalisability of results. Finally, the reviewers' comments on study quality or generalisability (in relation to the TAR scope) of their results were recorded.

Results

The publications search for cost analyses and economic evaluations of CRT yielded 70 published papers or conference abstracts. Of these, copies of 13 full publications were obtained (those publications which, on the basis of their title and abstract, might meet the review inclusion criteria already described). Of these, only six were

TABLE 24 *Summary of published economic evaluations of CRT*

Study	Study type	Analysis type	Country and price year	Comparators	Perspective
Banz, 2005[111]	Decision model	CUA	Germany, 2002	CRT-P vs OPT	Payer and society
McAllister *et al.*, 2004[114]	Decision model	CUA	USA, 2003	CRT-P vs OPT	Payer
Nichol *et al.*, 2004[112]	Decision model	CUA	USA, 2003	CRT-P vs OPT	Payer
Feldman *et al.*, 2005[110] (abstract)	Trial + modelling extension of COMPANION trial, data to 5 years	CEA	USA (no price year)	CRT-P vs OPT CRT-D vs OPT	Payer (Medicare)
Fattore *et al.*, 2005[113]	Decision model	CUA	Italy, 1997	CRT-P vs OPT	NHS (SSN[a])
Feldman *et al.*, 2005[109]	Trial + modelling extension of COMPANION trial, data to 7 years	CUA	USA, 2004	CRT-P vs OPT CRT-D vs OPT	Payer (Medicare)
Calvert *et al.*, 2005[108]	Trial-based (CARE-HF)	CUA and CEA	Europe (12 countries), **but** UK costs (no price year)	CRT-P vs OPT	Payer

[a] Servizio Sanitario Nazionale.

ultimately judged to be full economic evaluations according to our inclusion criteria. They were all published in 2004 or 2005, but the price years of some analyses went back as far as 1997.

Study types and settings

As shown in *Table 24*, four of the published analyses were based on decision models; one by Calvert and colleagues[108] was directly based on the CARE-HF trial, and the two studies by Feldman and colleagues[109,110] were modelling-based extensions to analyses of COMPANION trial data. All but one of the seven studies included a CUA [i.e. they estimated the incremental cost per quality-adjusted life year (QALY)]. *Table 79* in Appendix 6 shows more details of the study designs and settings of the included studies.

None of the studies were conducted from the perspective of British society or the UK NHS. Four are US-based, one is a 'preliminary' or illustrative analysis from Germany, one is from Italy and one based on the CARE-HF study is from a 12-country pan-European perspective. Only the two analyses based on the COMPANION trial, by Feldman and colleagues,[109,110] estimated the cost-effectiveness of CRT-D devices; all the other analyses compared optimal pharmacological therapy with CRT-P.

Most of the published studies were conducted with financial support from the manufacturers of CRT devices, and some also involved co-authors employed by such companies. A notable exception to this is the study by Nichol and colleagues,[112] which was commissioned by the US Agency for Healthcare Research and Quality (AHRQ) from the University of Alberta Evidence-based Practice Centre (Edmonton, Alberta, Canada).

Results: cost-effectiveness of CRT-P versus OPT

The base case analyses of the US-based CUAs estimated the incremental cost per QALY gained by the use of CRT-P devices (compared with OPT or medical therapy) to be variously US$19,600,[109] $90,700[114] and $107,800[112] per QALY (*Figure 7*). Nichol and colleagues' model-based analysis has a lifetime horizon of the remaining life of the modelled person, whereas the modelling extension of the COMPANION trial data by Feldman and colleagues extended the trial results for only 7 years.

Table 79 in Appendix 6 shows the full cost-effectiveness results for all six included economic evaluations.

In the three Europe-based CUAs, the base case incremental cost per QALY gained by the use of CRT-P devices (compared with OPT or medical therapy) varies more than three-fold, between €19,319[108] in the CARE-HF trial-based analysis and €63,225[113] per QALY from an Italian NHS perspective (*Figure 8*).

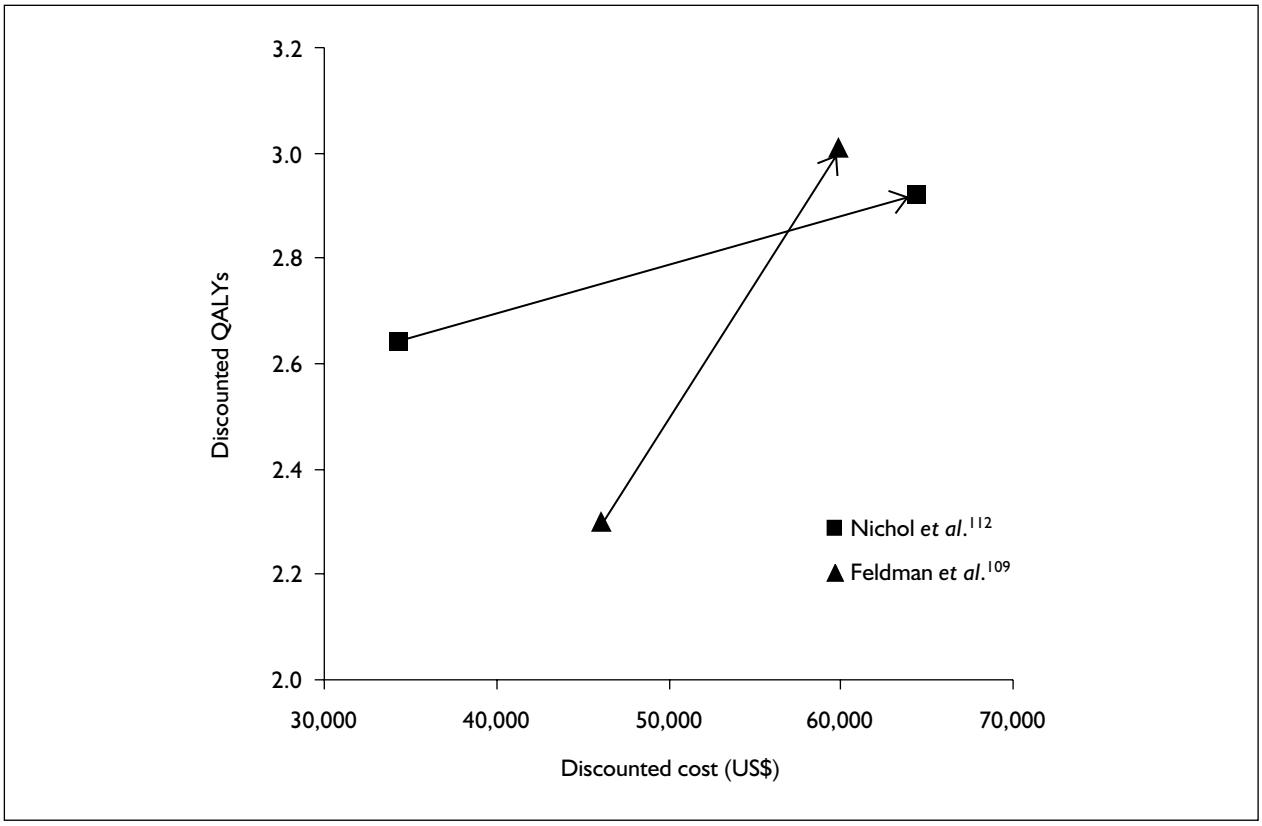

FIGURE 7 *US-based cost and utility estimates of CRT-P versus OPT. The direction of the arrow indicates movement from OPT to CRT-P.*

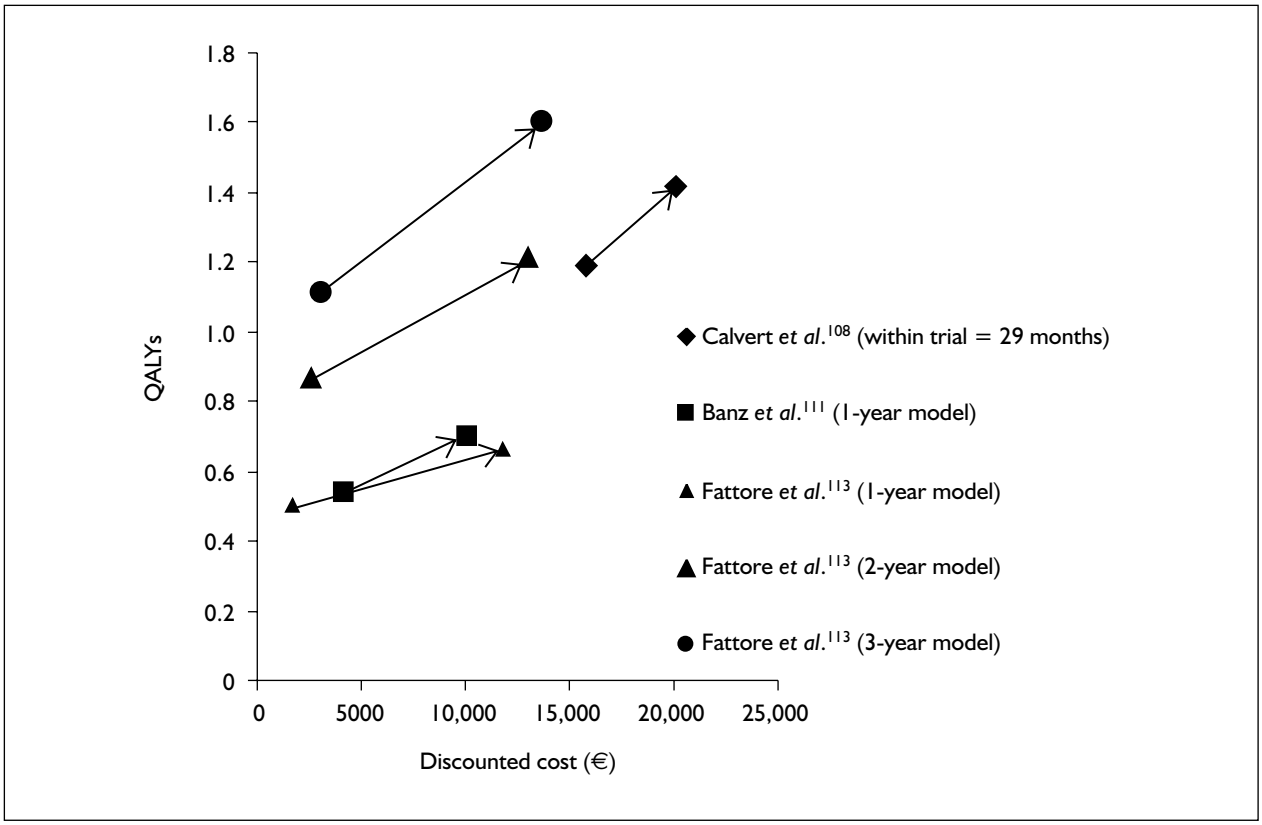

FIGURE 8 *Europe-based cost and utility estimates of CRT-P versus OPT. The direction of the arrow indicates movement from OPT to CRT-P.*

In the Italy-based study by Fattore and colleagues,[113] as in the US-based CEA of the COMPANION trial,[109] the analyses with longer time horizons had progressively more favourable cost-effectiveness ratios. In the Fattore study, increasing the time horizon of the analysis from 1 to 3 years reduced the ICER from €63,225 to €21,720, whereas data from the Feldman study show that increasing the time horizon from 2 to 7 years reduced the (undiscounted) ICER by a similar proportion, from $109,700 to $38,500. These two findings suggest, first, that the results from within-trial or short time horizon CEAs should probably be treated with considerable caution. Second, however, those studies which employ longer time horizons (e.g. 5 years or longer) require careful scrutiny of the methods for extrapolating beyond trial clinical and resource use data.

Results: cost-effectiveness of CRT-D versus OPT

The only published economic evaluation of CRT-D versus OPT[109] reports a base case discounted ICER of US $43,000 per QALY compared with OPT alone. However, the probabilistic sensitivity analysis for the ICER of CRT-P versus OPT ranged from –$203,800 to +$225,000 per QALY (95% CI), with around 20% of simulations resulting in CRT-D being both more costly and less effective than OPT. This demonstrates the considerable uncertainty in the analysis, particularly surrounding the estimated QoL benefits of implanting CRT-D devices.

Like Calvert and colleagues' economic analysis (alongside the CARE-HF trial),[108] this study imputed QoL preference weights (utilities) using trial data from the disease-specific QoL instrument (the MLWHF questionnaire scores; conversion algorithm from Havranek and colleagues[115]).

Feldman and colleagues[109] do not present incremental results for CRT-D versus CRT-P. However, using data presented in Table 4 of their paper, it is possible to calculate the undiscounted ICERs of moving from OPT to CRT-D and from CRT-P to CRT-D (*Table 25*). However, this analysis should be treated with some caution since (a) it relies on an effectiveness difference between CRT-P and CRT-D which may not be statistically significant and (b) this study involved the same types of patients receiving CRT-D and CRT-P without consideration or selection of patients more likely to benefit from an ICD as well as CRT.

Assessment of the industry submission

Industry-submitted economic evaluations

There was one joint industry-submitted economic evaluation (on behalf of five companies: Biotronik UK, Guidant, Medtronic, Sorin Biomedical CRM UK and St Jude Medical UK), and also a separate submission to NICE by Guidant (*Table 26*).

The joint industry submission documents did not make clear which of the four analyses should be regarded as the reference case, so we have assumed that both the CARE-HF trial-based analysis (analysis 1) and the analysis that is based solely on US data (analysis 3) are irrelevant to the current decision context in which both UK data and longer term cost and effectiveness implications need to be considered.

It should be noted that none of the industry-submitted analyses directly compared the cost-effectiveness of CRT-D with CRT-P, despite the specification of this comparison in the NICE project scope as a policy-relevant comparison. The joint submission claims that this omission is because the relevant clinical evidence "is not supported by the clinical community" and would

TABLE 25 *Incremental cost-effectiveness of CRT-D*

	Cost (US$)	QALYs	Incremental cost cf. OPT (US$)	Incremental QALYs cf. OPT	Incremental cost cf. CRT-P (US$)	Incremental QALYs cf. CRT-P
OPT	46,021	2.48				
CRT-P	59,870	3.26				
CRT-D	82,236	3.42	36,215	1.03	22,366	0.16
Undiscounted ICER: CRT-D vs OPT			38,527 per QALY			
Undiscounted ICER: CRT-D vs CRT-P					139,788 per QALY	

TABLE 26 *The joint submission summarised four different analyses (see below)*

Submission	Analyses presented	Analysis type	Source of effectiveness and resource use	Reported elsewhere?
Joint submission	1. CRT-P vs OPT	Within trial (19.4 months)	CARE-HF trial	Calvert *et al.*, 2005[108]
	2. CRT-P vs OPT	Modelling-based trial extension (5 years)	CARE-HF trial and case series from Good Hope Hospital, Birmingham	Leyva *et al.* (draft paper)
	3. CRT-D and CRT-P vs OPT	Modelling-based trial extension (5 years)	COMPANION trial, US DRG unit cost data	Feldman *et al.*, 2005[109]
	4. CRT-D and CRT-P vs OPT[a]	Modelling-based trial extension (5 years)	COMPANION trial data, but with UK HRG unit costs	No
Guidant submission	CRT-D and CRT-P vs OPT[a]	Modelling-based trial extension (5 years)	COMPANION trial data, but with UK HRG unit costs	No

DRG, Diagnosis Related Group; HRG, Healthcare Resource Group.
[a] These two analyses are identical, except for being reported in different levels of detail.

therefore lead to an analysis that is not scientifically robust.

Joint industry-submitted economic analysis of CRT-P based on CARE-HF

This is a two-comparator (CRT-P versus OPT) discrete event simulation model, using clinical effectiveness data from the CARE-HF trial, with resource use data and risks of re-implantation from a cohort of 171 patients treated with CRT at the Good Hope Hospital (Birmingham, West Midlands, UK) and followed up for a mean of 30 months. The industry submission described this as being in a "naturalistic setting", as opposed to being alongside a clinical trial. The analysis was conducted from an NHS perspective over a 5-year time horizon, with QALYs as the main outcome measure.

Some detail of the methods and results of this analysis were available as a draft journal article which was provided with the main industry submission. However, the diagrams and tables to support this paper were not supplied, so the following sections have not been informed by any detailed appraisal of either the structure of the model or the parameter values used. This analysis was conducted by a team comprising clinical researchers based at the Good Hope Hospital (Birmingham, West Midlands, UK; Leyva and colleagues), decision analytic modellers/consultants at the Caro Research Institute (Concord, MA, USA) and researchers employed by Medtronic.

Overall appraisal

Overall, this economic analysis meets most of the important methodological criteria stipulated by NICE for health technology assessment.[116] This was made more awkward to judge because the full details of the analysis were not available in a single report, and also the figures for the supporting paper (by Leyva and colleagues) were missing.

Major limitations

The time horizon of 5 years, although usefully longer than the duration of any of the CRT trials, may be inadequate to capture the full costs and health outcomes due to CRT-D or OPT. By the end of the simulation, some 53% of OPT patients and 65% of CRT-P patients were still alive. Furthermore, a relevant aspect of this assessment that is not addressed is the need to replace devices or leads that have become faulty or infected or to replace units whose batteries have depleted.

Other limitations

It was not made clear why resource use data from the UK patients in the CARE-HF trial were not used (NB: the CEA of the CARE-HF trial suggests that such resource use data were collected[108]). For comparison, CARE-HF resource use data from the UK treatment centres should at least have been presented alongside the analysis using the Good Hope Hospital data, where implantation failure rates and other complication rates may have differed.

Likewise, it was not well justified why the CARE-HF survival data were used in preference to a systematic review/meta-analysis of the literature.[66]

The representativeness of this single-centre submission is unclear and therefore the generalisability of the analysis is questionable.

Finally, the methods for the derivation and extrapolation of utility values might be questioned, given the poor correlation between MLWHF scores and EQ-5D.

Joint industry-submitted economic analysis of CRT-P and CRT-D based on COMPANION

A decision tree model built in Microsoft Excel (Microsoft, Redmond, WA, USA) captures the two basic events of all-cause hospital admissions and death. The model was structured to allow comparison of OPT with CRT-P or CRT-D. Survival and QoL data were taken and extrapolated from the COMPANION trial. The cost and risk of hospitalisations due to all causes were also taken from the COMPANION trial [using clinical expert opinion to map US DRG groupings on to NHS Healthcare Resource Groups (HRGs)]. Costs of devices and implantation were taken from the unpublished paper by Leyva and colleagues (based on a cohort of CRT recipients at the Good Hope Hospital).

The observations below are based on a close reading of the combined industry submission to NICE. Where necessary, this was supported by reference to the separately submitted more detailed report of the same analysis by the Healthcare Analytics Group of United BioSource Corporation (London, UK) for Guidant (author: R Brown and colleagues, dated 16 May 2006).

Overall appraisal

Overall, this economic analysis meets most of the important methodological criteria stipulated by NICE for such health technology appraisal.[116]

Major limitations

The time horizon of 5 years, although usefully longer than the duration of any of the CRT trials, may be inadequate to capture the full costs and health outcomes due to CRT-D or OPT. By the end of the simulation some 35% of OPT patients, 45% of CRT-P patients and 51% of CRT-P patients were still alive. Furthermore, an inevitable aspect of this health technology is the need to replace devices or leads that have become faulty or infected or to replace units whose batteries have depleted (which is probably an even more frequent event for people fitted with CRT-D devices).[6,71,76,81,89]

Other limitations

The reliance on the Havranek algorithm for translating MLWHF scores into utilities (which was also used in the trial-based CEA by Feldman and colleagues[109]) is a limitation of this analysis, given the very weak association between utilities and these scores ($r^2 = 0.1$).[115] For comparison, the visual analogue scores and SF-36 scores in the Havranek study had substantially better associations with the measured utilities ($r^2 = 0.30$ and 0.24, respectively). Moreover, these utilities were derived from a sample of people with HF rather than members of the general public.

Economic evaluation submitted by Guidant

The economic evaluation separately submitted by Guidant included an abbreviated (four-page) summary of the same CEA conducted by the Healthcare Analytics Group of United BioSource Corporation. Since this has already been described and appraised in the previous section, all the same observations apply.

Summary of industry-submitted economic analyses

Apart from a lack of clarity concerning which of the submitted analyses should be considered as the reference case analyses for this TAR, in general, the main joint industry submission report, its supporting documentation (notably the unpublished paper by Leyva and colleagues and the report by United BioSource Corporation for Guidant) are good descriptions of what appear to be reasonable quality model-based analyses.

The choice of the relatively short (5-year) time horizon, although superior to not extending the trial results, is questionable. In particular, it leads to an omission of the recurring costs of battery replacement and other complications that require new units, new leads or new whole device systems to be implanted. It is not clear whether the combined impact of increasing the time horizon of analyses and including the cost of regular device replacement would increase or decrease the ICERs presented.

There are also some large disparities between the two industry-submitted analyses in the extrapolated survival to 5 years. The reliance on the Havranek algorithm for deriving utility weights from MLWHF scores may have also helped to generate the favourable cost-effectiveness results of the analysis based on the COMPANION trial.

Finally, the joint submission and the separate submission from Guidant contained only weak justification for not directly comparing the cost-effectiveness of CRT-D and CRT-P. Although the patient groups that are clinically eligible for each

type of device will be slightly different, they were sufficiently similar to be randomised in the COMPANION trial, and decision modelling could allow exploration of the effectiveness of CRT amongst different patient groups (e.g. those at different age or perceived risk of SCD). Tables of the joint industry submission with NICE methodological guidance can be found in Appendix 7.

Summary of review of economic evaluation and industry submissions

1. Seven full economic evaluations (according to our criteria) were found. None were from a British society or UK NHS perspective.
2. There was one joint industry submission to NICE and one single submission from Guidant (which was a subset of the joint submission).
3. The joint submission presented two analyses that were relevant to the present appraisal. One used a discrete event simulation model which extended the CARE-HF trial results to 5 years. This gave estimated ICERs for CRT-P versus OPT of £13,142 per QALY.
4. The other analysis in the industry submission used a decision tree model which extended the COMPANION trial results to 5 years. This analysis gave estimated ICERs for CRT-P versus OPT of £2818 per QALY and for CRT-D versus OPT of £22,384 per QALY. CRT-P versus CRT-D was not reported.

PenTAG cost–utility model

We aimed to assess, based on available data, the cost–utility associated with the use of CRT. Three pairwise comparisons were made: CRT-P and CRT-D were individually compared directly with OPT alone and CRT-P was compared with CRT-D. Although these pairwise comparisons are those apparently demanded by the NICE appraisal scope (and were therefore also a feature of the protocol for this review), we acknowledge that the most useful cost–utility comparison is actually that between all three comparators. Furthermore, the validity of making the cost–utility comparison between CRT-D and OPT is questionable, given that the obvious comparator for CRT-D should be the next cheapest and next most effective alternative treatment for this patient group, i.e. probably CRT-P.

NB: It should be remembered that these model-based analyses are modelling **policy** decision problems rather than **clinical** decisions. They therefore simulate patients under hypothetical scenarios in which access to certain health technologies either is or is not available within the NHS. Therefore, for example, people receiving OPT under the hypothetical scenario that CRT-D has not been made available within the NHS cannot later be provided with CRT-D if over time they develop major AF.

Methods

We based the model on the possible events that people could have if they had either a CRT-P or CRT-D implanted or if they remained on OPT alone. This approach was preferred to basing the model on the natural course of the syndrome of HF because this would have meant predicating it on the NYHA taxonomy, a subjective measure of functional ability, which would not have enabled us to address the decision problem adequately.

The population, a mixed age cohort, is modelled until death. Costs and benefits are discounted at 3.5%.[116] The costs and benefits of CRT were estimated using a state transition (Markov) model.[117] This approach was chosen for three reasons. First, in order to assess accurately the costs and benefits of each intervention, a lifetime time horizon was felt necessary. Second, only secondary information was available to populate the decision model. Third, the ability to conduct probabilistic sensitivity analyses (PSAs) is a major advantage. Given these three points, the Markov approach was felt to be the appropriate choice.

The model was developed in Microsoft Excel with structure informed by expert clinical opinion on the management of HF. The costs and benefits associated with OPT alone were also estimated using a version of the same model.

The base case uses resource costs for 2005, with the exception of drug costs, which are taken from the latest BNF[118] (2006). The perspective is of the UK NHS. The model estimates the costs (in UK pounds) and benefits (in QALYs) resulting from each of the comparisons. Where an intervention is estimated to be both more effective and more costly than a given comparator, an ICER is calculated. This is the net difference in costs divided by the net difference in health outcomes or QALYs. The incremental analysis shows the pairwise difference in cost and benefits for different treatments.

Following on from a description of the construction and parameterisation of the model, outputs relevant to each research question were reported, and for each pairwise combination of

CRT-P, CRT-D and OPT an extensive analysis of parameter uncertainty was performed. This included one-way sensitivity analyses and threshold analyses of the key input parameters.

For each of the three pairwise comparisons, a PSA was performed to assess decision uncertainty. A PSA was also used for a three-way comparison (CRT-P versus CRT-D versus OPT). The probability that the treatment is cost-effective at various willingness-to-pay (WTP) thresholds was derived. Finally, a value of information analysis was performed for each pairwise comparison to inform future research into CRT usage.

Relevant patient population(s)

Cohorts of people with HF due to left ventricular systolic dysfunction and a QRS duration >120 ms were modelled for their lifetime (age range 30–90 years). The gender, age and clinical characteristics of the cohort reflect the distribution of HF across the general population. The effect of changes in the cohort gender and age mix on the cost-effectiveness of each treatment was explored as part of the sensitivity analysis.

Framework (method of synthesis)

Cohorts of people with different starting ages were modelled independently and results were pooled to produce a single deterministic ICER. The weightings applied were selected to match as closely as possible the underlying population of people with HF. A cycle length of 4 weeks was used in order to suitably capture the complexity of the process and to maintain flexibility in the model. The impact of running the model using different time horizons was assessed in sensitivity analysis. The short model cycle meant that no half cycle correction was necessary.

Determination and modelling of treatment pathways

The NYHA classification of the natural history of disease progression in people with HF was not explicitly incorporated into the model's health states. However, the different utilities and costs (of OPT medication) are included in the model, within states, using specified distributions of people across the NYHA classes at different time points and with and without CRT (see 'Utilities by NYHA subclass', p. 64). Simplified versions of the CRT-P model were produced to allow for differences in costs and treatment options with CRT-D and OPT to be assessed.

The key events included in the model are shown in *Table 27*. The possibilities of surgical failure and device upgrades were included. Surgical failure is defined as a technically unsuccessful procedure, in contrast to patient non-response to a technically successful procedure.

The events in *Table 27* can potentially occur with CRT-P, CRT-D or ICD options. It was therefore necessary to develop submodels for each of the three device options in addition to OPT.

Patient pathways for people who have received a CRT-P device

People who receive a CRT-P device can potentially receive an upgrade to either a CRT-D or an ICD device or regress to OPT (*Figure 9*). People on OPT can potentially receive an upgrade to an ICD

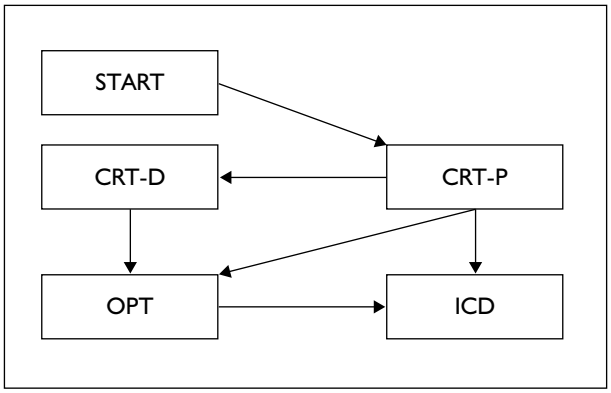

FIGURE 9 *Potential device pathways for people in the CRT-P submodel*

TABLE 27 *Key events in the PenTAG model*

Device-related event	Other events
Routine device replacements	Hospitalisation due to HF
Perioperative complications	Hospitalisation due to arrhythmia
Infections	Heart transplant
Device upgrades[a]	Surgical failure
Left lead dislodgements	Death

[a] ICDs were incorporated into the model as a potential treatment option (device upgrade).

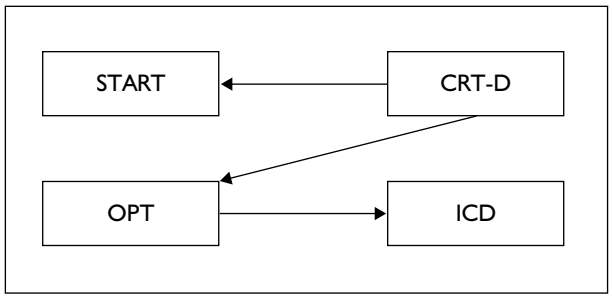

FIGURE 10 *Potential device pathways for people in the CRT-D submodel*

device. Should a person ever receive an ICD device, they will not revert back to OPT alone.

People who receive a CRT-D device can potentially regress to OPT and people receiving OPT can go on to receive an ICD (*Figure 10*). As before, people who have an unsuccessful operation continue to receive OPT alone.

Figure 11 shows the device pathways in the OPT model. Here the only potential upgrade option is to an ICD device.

Submodel probability trees

Transitions between health states used in the Markov model are driven by a sequence of probabilities. However, it is possible to arrive in a particular health state as a result of a number of events. Therefore, the required transition probability must take into account all of these events. In order to visualise the potential pathways, it is necessary to build probability trees.[117] Each state in the Markov model will have an associated tree, with feasible transitions between any two particular health states being represented as a pathway through the tree. The associated transition probability is calculated by multiplying the probabilities associated with the individual branches. Where there are multiple pathways between two states, the transition probability is the sum of the individual pathway probabilities.

A selection of the probability trees used to generate the PenTAG model is shown in Appendix 7. In these diagrams, circular junctions are chance nodes; the proportion of people experiencing different events at these chance nodes is based on probabilities drawn from the literature or expert opinion. The health state at the beginning of the tree is the start state. End states are at the end of the tree and are labelled 'To health state name'. Where health states are not represented, transitions from the start state are not possible. The probabilities attached to each of the lines may be set to zero. This is interpreted as the event not being possible during a particular cycle.

Influence diagrams for each submodel

Health states

Within a Markov model, people occupy one of a finite number of discrete health states. Within each model cycle, people make at most one state movement. The values attached to each transition during each model cycle are derived from event probabilities. These probabilities were based where possible on published data or, where no data were available, on expert opinion. The impact of changes in these probabilities on the final cost-effectiveness estimates was explored using sensitivity analyses. *Table 28* lists the health states used in the PenTAG model.

Influence diagrams

In the influence diagrams in *Figures 12–14*, the different submodels are represented as the large shaded boxes. Within these large boxes are smaller (white) boxes, which represent the individual health states used (e.g. 'Stable CRT-P'). Possible movements between these states are represented by arrows.

The influence diagrams contain both thick and thin arrows, representing different types of transitions. Solid single-lined arrows represent feasible transitions between individual pairs of health states, with movement being in the direction of the arrow. A double-headed arrow indicates that movement in both directions is possible. In general, transitions involve someone either experiencing some form of adverse event (and therefore moving into the relevant health state) or experiencing no event (movement from the state corresponding to an adverse event to the relevant 'stable' state).

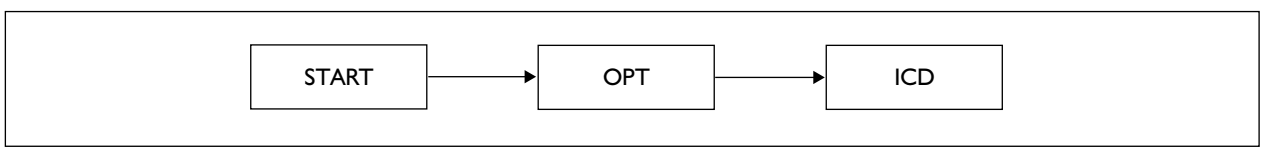

FIGURE 11 *Potential device pathways for people in the OPT submodel*

TABLE 28 *List of health states used in the PenTAG model*

Health state(s)	Description
PSUR	Original CRT-P device implanted
DSUR	Patient has an operation to upgrade the original CRT-P device to a CRT-D device
ISUR	Patient has an operation to implant an ICD device
PCOM, DCOM, ICOM	Patient experiences some form of postoperative complication following pacemaker implantation
NPB, NDB, NIB	Patient has an operation to perform routine maintenance of pacemaker device (e.g. device change)
PStb, DStb	Patient has a CRT device and experiences no adverse events during the model cycle
OStb	Patient receives OPT only (no pacemaker or defibrillator in use) and experiences no adverse events during the model cycle
IStb	Patient has an ICD device and experiences no adverse events during the model cycle
POP, DOP	Patient experiences a CRT-related infection
IOP	Patient experiences an ICD-related infection
PLD, DLD, ILD	Patient experiences a lead displacement
PHF, DHF, OHF, IHF	Patient is hospitalised for HF
TRP	Patient is hospitalised for HF and receives a heart transplant
DFS	Patient is dead as a result of either the original operation to implant CRT-P device or any subsequent operation
SCD	Patient is dead as a result of sudden cardiac causes
HDTH	Patient has died as a result of worsening HF
ODTH	Patient is dead as a result of other, non-cardiac-related causes

The solid double-lined arrows represent movement from **any state** inside the larger shaded boxes to a particular health state (e.g movement from any state in the CRT-P submodel to the routine box change state (NPB). Dashed double lines represent movement from a particular state to any state in a submodel [e.g from CRT-P perioperative complications (PCOM) state to any state in the CRT-P submodel]. Circular arrows in the corner of a health state refer to a person staying in a particular state for a further cycle. States that do not have circular arrows are tunnel states and therefore state occupancy only lasts 4 weeks (one cycle). All people who are in one of these tunnel states at the start of a cycle begin the subsequent cycle in a different one. Transplantation is a different form of tunnel state. People who enter this state remain there until they die. The model also contains four 'sink states' used to represent different modes of death. Sink states are impossible to leave and once people enter them they remain there for the remainder of the duration of the model.

CRT-P

Figure 12 shows the influence diagram for the complete model used to derive estimates of costs and health benefits associated with CRT-P devices.

CRT-D

The influence diagram corresponding to the CRT-D model arm is shown in *Figure 13*.

People in the CRT-P or CRT-D arms of the model enter the initial surgery state (PSUR and DSUR) and have the respective device implanted. If this is successful, they go on to a stable state. However, if they experience complications, these have to be resolved before they enter the relevant CRT submodel.

During each subsequent cycle, a patient in the stable with CRT-P/D state (PStb/DStb) can experience a lead displacement or a CRT-related infection. They can also be hospitalised as a result of HF, experience an arrhythmic event or die. Correction of either lead displacements or CRT-related infections involves an invasive procedure. The PenTAG model assumes that some of these procedures may be unsuccessful and they also carry a small risk of death. If a procedure to remedy either of these two adverse events fails then the patient reverts back to receiving OPT alone in the CRT-P group or would continue with defibrillating capacity in the CRT-D group unless the device was explanted and not replaced.

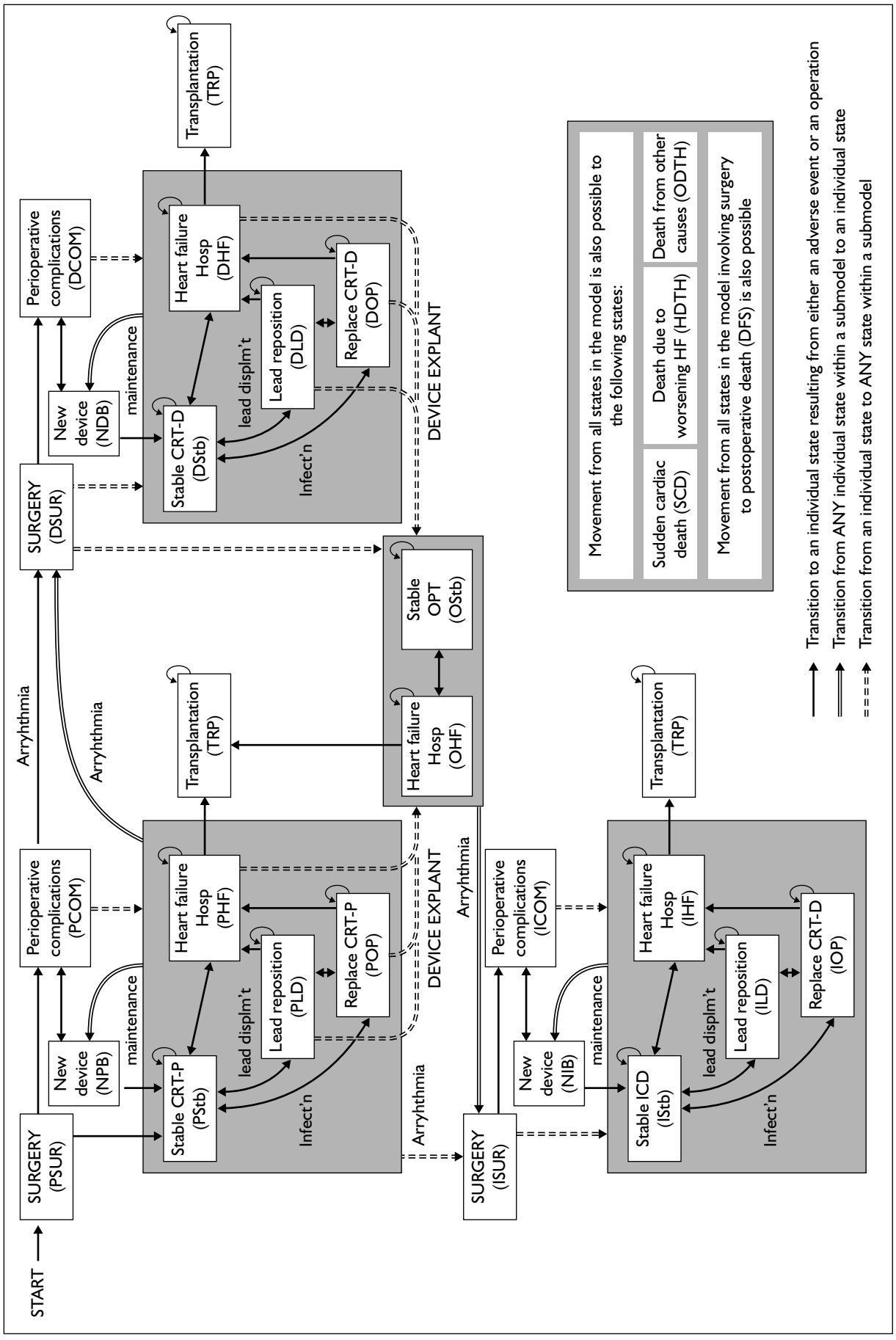

FIGURE 12 *Influence diagram for people in the CRT-P arm of the model*

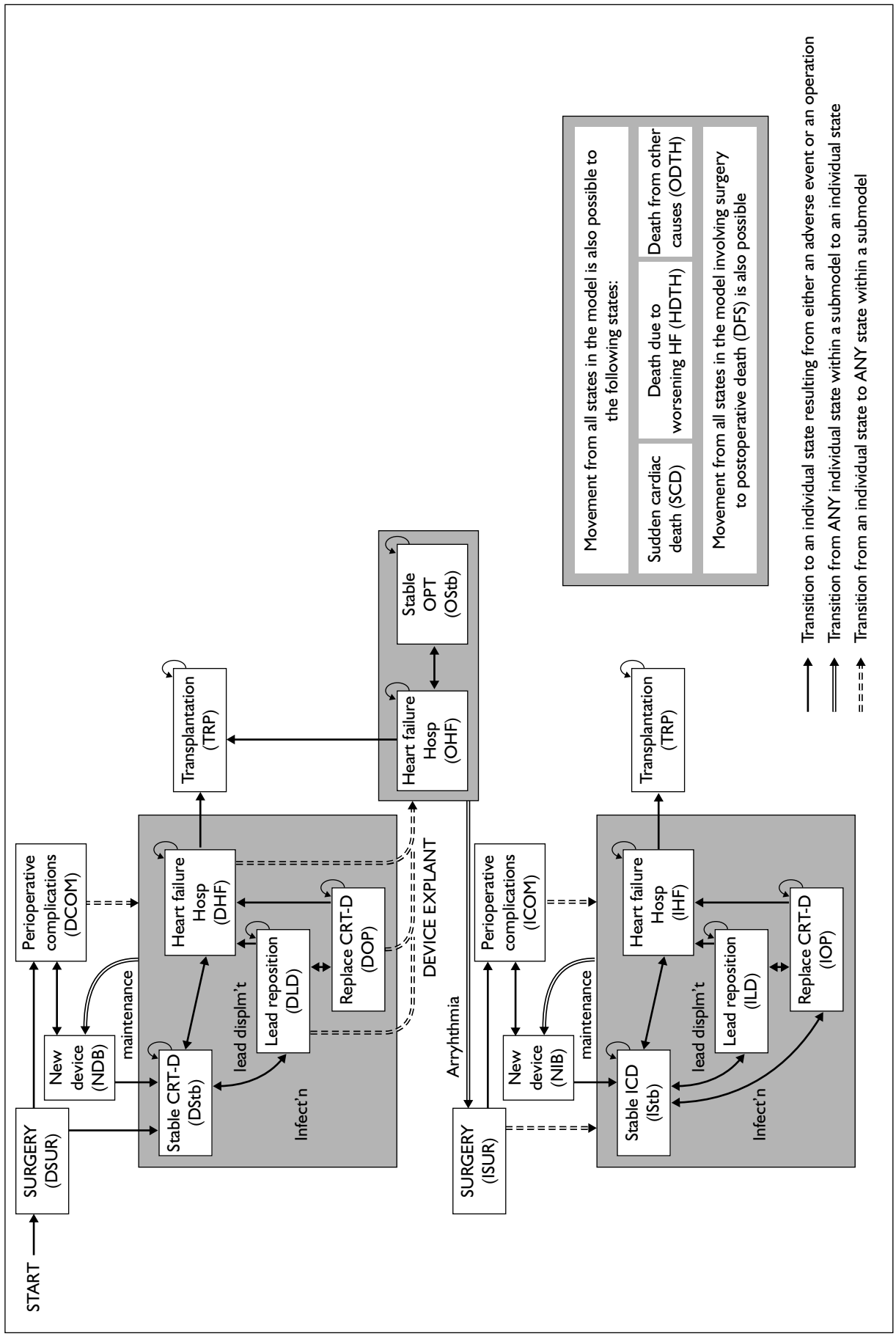

FIGURE 13 *Influence diagram for people in the CRT-D arm of the model*

Consequently, transitions to the 'stable on OPT' (SOpt) and 'hospitalisation with heart failure on OPT' (OHF) health states are possible every cycle.

People in whom surgery to correct either an infection or displacement is unsuccessful are considered to be in the OPT submodel and experience events accordingly. In particular, if they are hospitalised for HF they enter the OHF health state, and if they experience an arrhythmic event [ventricular fibrillation (VF) or syncopal ventricular tachycardia], they are eligible for an ICD and enter the ISUR state. Therefore, it is possible to move from having a CRT-P to an ICD in one cycle.

People with a CRT-P who are hospitalised as a result of worsening HF become candidates for either a CRT-D or a heart transplant. Transplant is only possible in people who have been hospitalised for HF during the previous cycle.

Transplantation is modelled as a quasi-sink state; once a patient enters it, they remain there until they die. The probability of death post-transplant is lower than in the general model, except in the first cycle.

CRT devices are assumed to work for a fixed period and all people who are still alive at the end of that period are sent back to a surgery state (NPB) in order to have a new device fitted.

If a patient with a CRT-P device experiences a serious arrhythmic event, and survives, an upgrade to a CRT-D is deemed necessary and is possible in every cycle regardless of previous state occupancy.

Once a patient has been given a defibrillator upgrade, they experience the same events as before, although with different probabilities.

Death as a result of worsening HF, sudden cardiac events or other causes can occur from all health states, including initial surgery or generator upgrade. The baseline rates, HRs and/or the RR associated with the first two causes of death in the CRT submodels compared with the OPT submodel have been derived from the systematic review. The risk ratio associated with these causes of mortality in people with an ICD device compared with those on OPT has been taken from a previous TAR.[119] The probabilities associated with HF and SCD are further modified using an age-related RR. This means that all-cause death is both age and time dependent (in terms of model cycles). Death from other causes was determined from UK population statistics.[23]

People who have an unsuccessful surgical procedure from any of the health states are simulated in the same way as those in the OPT arm of the model; they experience the risks and accumulate the costs and benefits of OPT. However, they remain a part of the CRT-P and CRT-D cohorts, i.e. costs and benefits continue to be counted within the CRT-P and CRT-D arms.

Optimal pharmaceutical therapy

Once a patient enters the OPT model, they may experience all of the patient-related events in *Table 27*, and if they have an arrhythmia are automatically given an ICD. People receiving an ICD device enter the ICD submodel, and remain there until they either receive a heart transplant or die.

The influence diagram for the OPT arm of the model is shown in *Figure 14*.

List of PenTAG model assumptions

Table 29 reports the main assumptions made in developing the models described above.

Time horizon

The model does not use a pre-determined fixed time horizon. For each different starting age, cohorts are followed until death (defined as less than one person alive) in the assessment of the deterministic headline ICER value. The effects of imposing fixed time horizons on the base case ICER are explored as part of the sensitivity analysis.

Model parameters

Age-dependent distribution of people with heart failure

HF is more common in men, so we have assumed a male:female ratio of 64:36 in the model.[1] The weighted average number of events in each year and the proportion of all events in each category are displayed in *Table 30*.

The last row of *Table 30* represents the sampling distribution for people's ages used in generating the composite ICER, that is, a weighted average of the individual age ICERs. This distribution is represented by the bar chart in *Figure 15*.

The summary statistics associated with the distribution defined in *Figure 15* [mean age

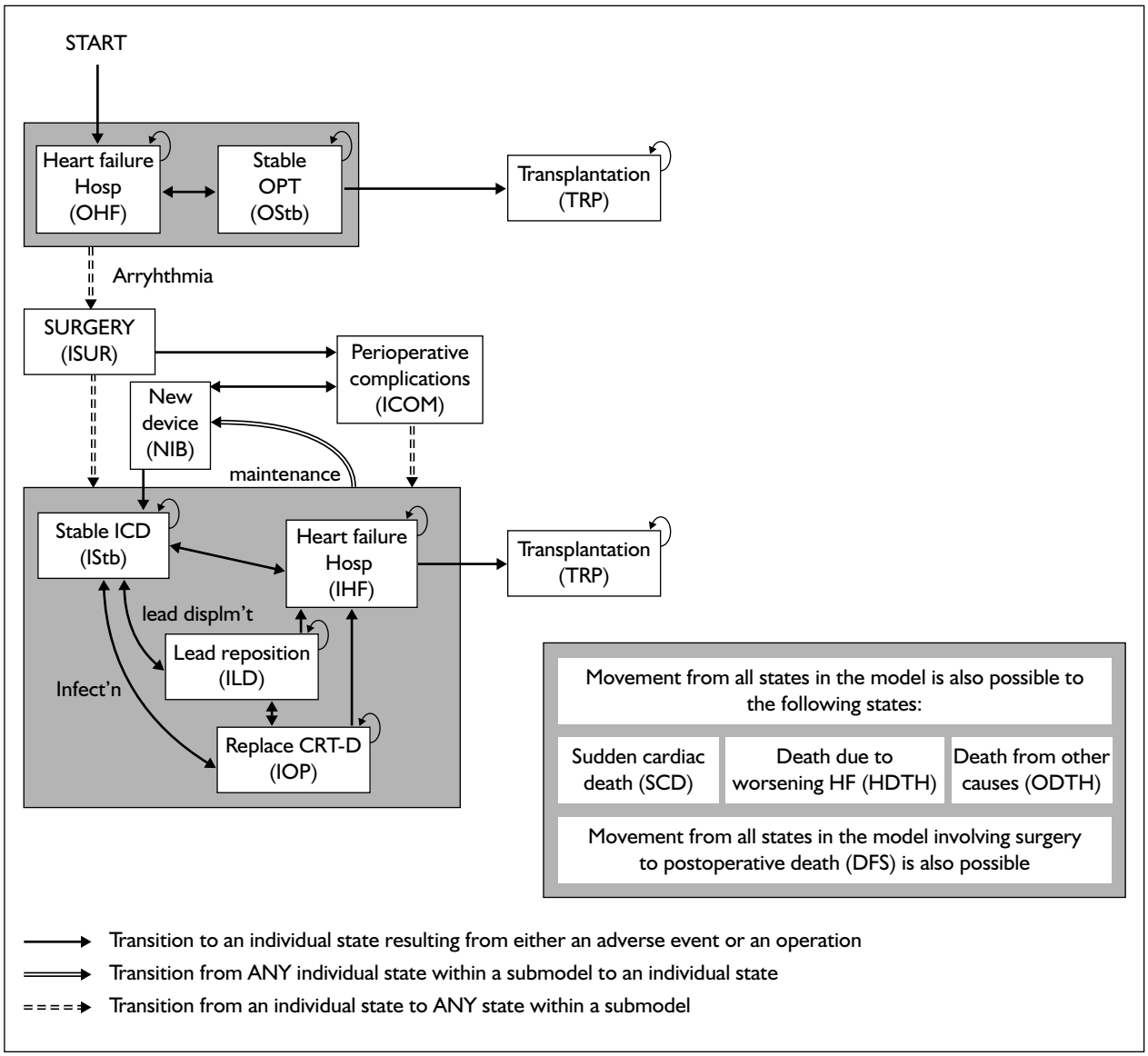

FIGURE 14 *Influence diagram for people in the OPT arm of the model*

73.9 years, standard deviation (SD) 11.8 years] broadly matches the age profiles of the major trials.[6,71,75,81,89]

Mortality

Mortality in OPT arm of the model

Baseline mortality

As the CARE-HF trial had the longest follow-up time[74] and UK data (n = 147, 18%), it was used to define the baseline population mortality. The mortality benefit of CRT over time was calculated using the survival curve from the OPT group in CARE-HF and the pooled HR.

Survival

Approximations of survival were produced from Kaplan–Meier curves using a Weibull distribution. An approximate hazard function for the curve can then be derived. Transition probabilities can then be calculated using standard techniques.[122] *Figures 16* and *17* show the data extracted from the published CARE-HF study as well as the fitted Weibull approximation.

The Weibull distribution is manipulated by adjusting the two defining curve parameters: the scale parameter (λ) and the shape parameter (γ). The curve was fitted using methods derived from regression analysis, so quality of fit was assessed using the R^2 statistic. The curve in *Figure 16* is an excellent fit (R^2 = 0.9861). The γ value (1.29, 95% CI 1.20 to 1.38) is greater than 1, implying that the probability of death as a result of HF, in people on OPT, increases with time. This curve in

TABLE 29 *Assumptions in the PenTAG model*

Assumption	Rationale
HRs and RRs are constant over the whole time horizon of the model, i.e. a proportional hazard can be assumed	Pooled values for all HRs were derived from results in the systematic review, and tests for the suitability of a proportional hazards model have been performed
Information from trial populations can be generalised to the population of people with HF and dyssynchrony	From an epidemiological perspective, HRs are robust to such movements and so the effect of this assumption is not expected to be large[120]
Treatment effects and rates of adverse events present in trials continue over the whole time horizon of the model (with the exception of lead displacement, which is assumed to have a lifetime risk of 10%)	The model time horizon is a lifetime but the longest follow-up is 36 months in CARE-HF.[121] This is a key assumption. The value for risk of lead displacement comes from expert clinical advice
During each cycle, people in each of the cohorts will have the same NYHA class mix as the trials in the TAR systematic review	A similar approach to that taken by Feldman *et al*.[109] and Calvert *et al*.[108] and which reflects CARE-HF and COMPANION trial experience
The rate at which events occur are constant and age independent with the exception of death (an event happening does not change the state of subsequent events)	Modeller assumption. Although this is a strong assumption, it is felt that this method would produce a more realistic event probability than if, e.g. the model was predicated on the number of people hospitalised
All except the most common and/or major adverse events can be ignored	Modeller assumption. Due to the rarity of the individual events excluded, we do not expect this assumption to have a major impact on either the headline or outputs
Non-response is implicitly included in the event probabilities	Modeller assumption. Due to the lack of information about non-responders in the literature, outcome data from trials on responders and non-responders are not reported
Transition probabilities, other than death, are not modified by age	A comparison of the range of ages of trial participants with the distribution of patients in the general population showed that data had been collected over the ranges containing a majority of people in the general population
Everyone with a CRT-P device who experiences a major arrhythmic event automatically receives a CRT-D during the next model cycle	Modeller assumption
Those in the OPT arm are not eligible for a CRT-D device, and must instead receive an ICD	Modeller assumption
Those with a CRT-D for whom CRT does not work for whatever reason will still have defibrillating capacity	Expert advice
Those with a CRT-D device will not have a severe arrhythmic event requiring hospitalisation or other costs as the defibrillator will prevent these	Modeller assumption
The probability of dying as a consequence of surgery does not depend on which device a patient has	Modeller assumption

TABLE 30 *Average incidence of heart failure in the general population*

	Age group (years)							
	25–34	**35–44**	**45–54**	**55–64**	**65–74**	**75–84**	**84+**	**Total**
Weighed average number of events	0.36	3	2.92	16.32	30.40	41.36	17.88	112.24
Proportion of all events happening in each age group (%)	0.32	2.67	2.6	14.54	27.08	36.85	15.93	100

Source: derived from data in Cowie and colleagues.[12]

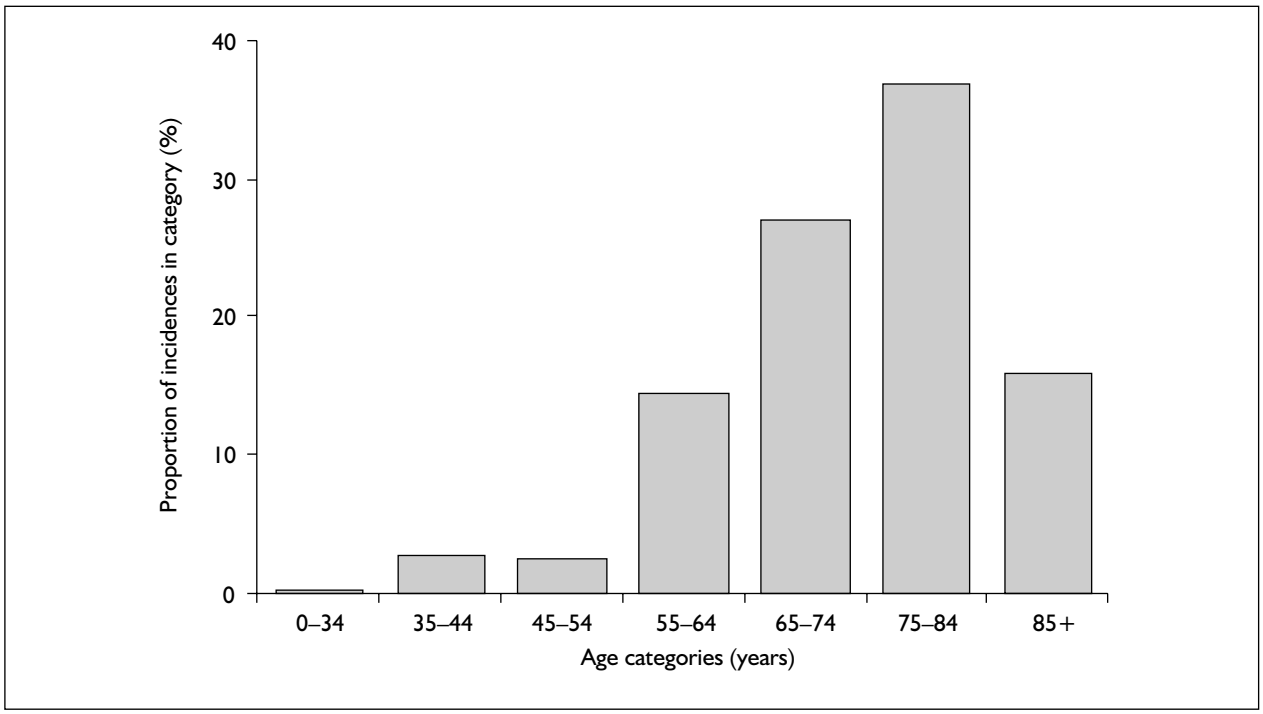

FIGURE 15 *Sampling distribution for age categories for generating the composite ICER*

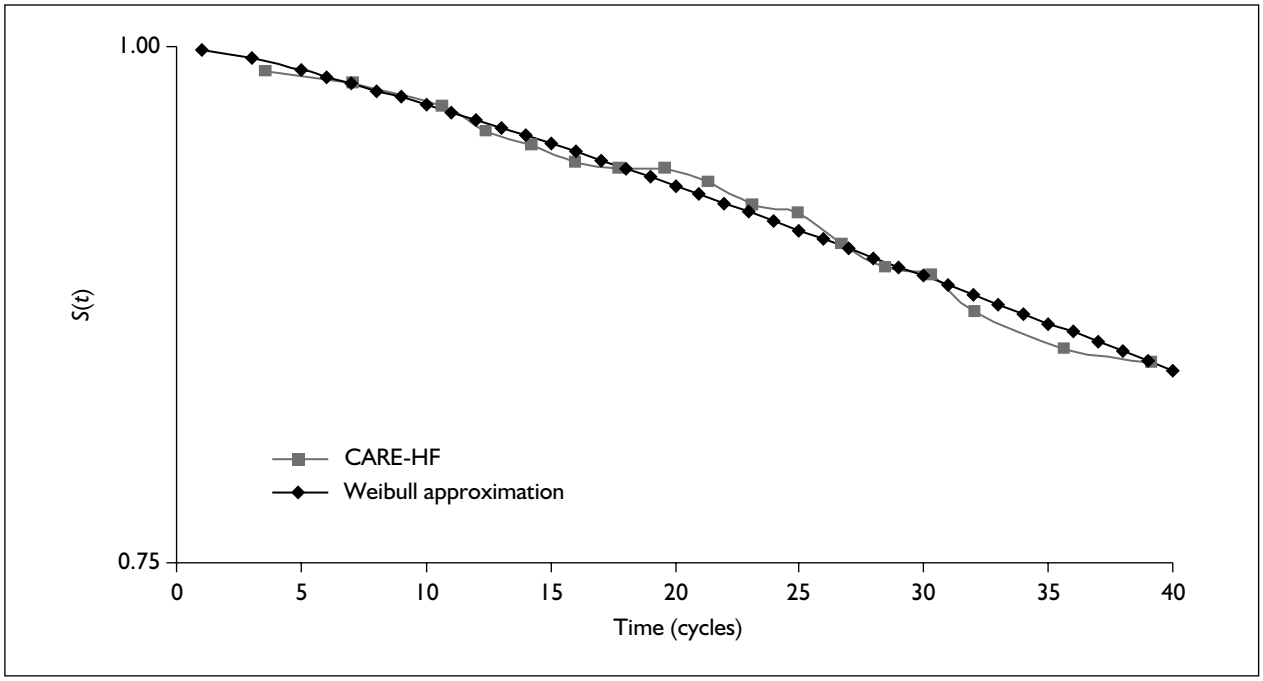

FIGURE 16 *Weibull approximation to published Kaplan–Meier curve for death due to worsening HF in the CARE-HF trial*

Figure 17 is also an excellent fit ($R^2 = 0.9828$). The γ value (1.21, 95% CI 1.14 to 1.28) implies that the probability of death from sudden cardiac causes in people receiving OPT increases with each model cycle.

Death from other causes

People with HF are also at risk of death from non-cardiac-related causes. We have made the assumption in modelling death from other causes that the risk of such an event is equivalent to the

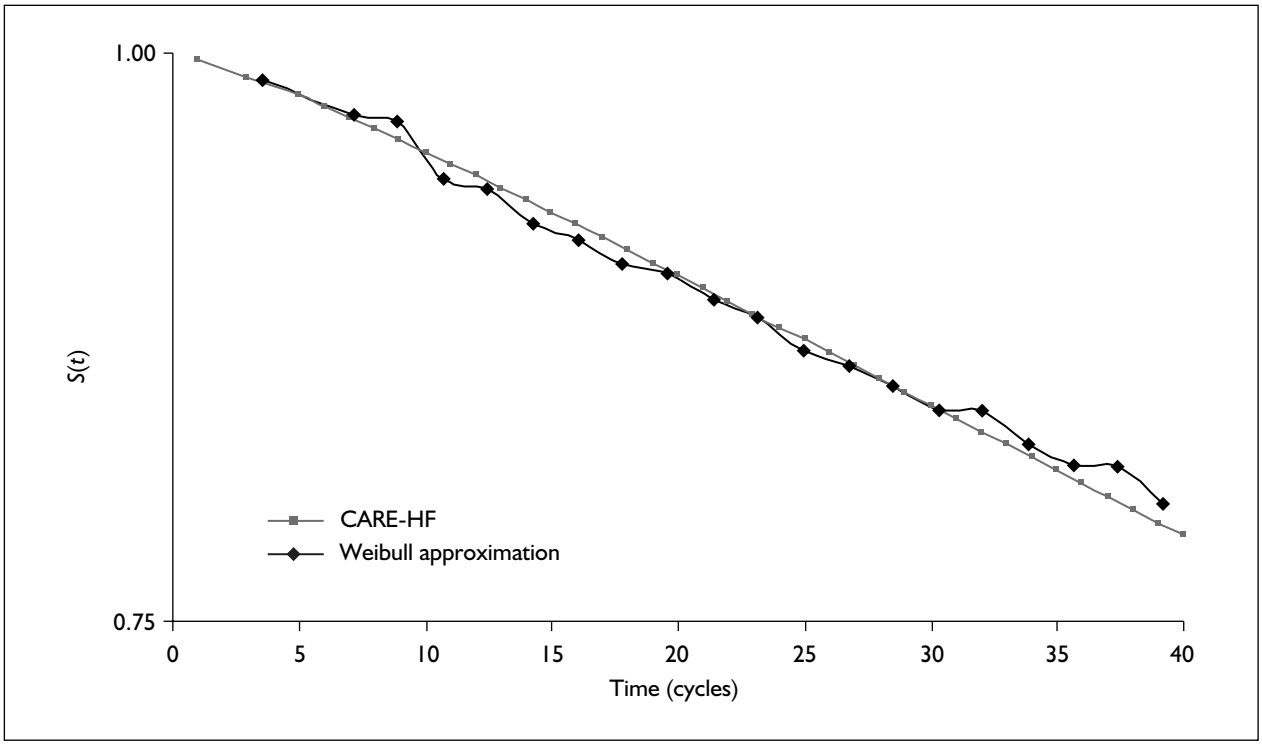

FIGURE 17 *Weibull approximation to published Kaplan–Meier curve for sudden cardiac death in CARE-HF trial*

TABLE 31 *Annual rates of non-cardiac-related mortality in England and Wales*

	Age group (years)							
	15–24	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**	**75–84**	**85+**
Annual male death rate (events per 1000 people)	1.2	0.8	1.3	2.4	5.8	15.9	46.0	129.0
Annual female death rate (events per 1000 people)	0.5	0.4	0.9	2.1	4.8	11.7	33.9	113.9
Model death rate (events per 1000 people)	1.0	0.7	1.1	2.3	5.4	14.4	41.7	123.6

Source: Office of National Statistics, 2003.

value from the general population. For the purposes of modelling, we have defined 'Death from other causes' to be all deaths not allocated an ICD-10 code I00–I50 inclusive. The Office of National Statistics (www.statistics.gov.uk) keeps detailed mortality records for people in England and Wales, and the values used to parameterise the model are based on the 2004 mortality survey. *Table 31* shows the annual mortality stratified by age and sex. These values are weighted using the assumed male–female mix to obtain an annual rate for people in the PenTAG model. From these weighted rates, the age-dependent cycle transition probabilities used in the model can be derived.[23]

Risk ratios applied to base-case death probabilities

The following section describes how the HRs and RRs for mortality in the PenTAG model were derived.

Derivation of age-dependent mortality hazard ratios

The model estimates the cost-effectiveness of a particular age and sex cohort in order to derive the ICER for different age categories. It then combines them to produce a single cost-effectiveness ICER for each device assuming a mixed age cohort. To do this, it is necessary to make the model outputs responsive to changes in

TABLE 32 *Modified age-dependent hazard ratios for people previously hospitalised with heart failure, derived from information presented by Shahar and colleagues*[123]

Age group (years)	HR	95% CI	Source
18–64	0.62	0.54 to 0.72	Derived from information in Shahar *et al*.
65–74	Ref.	–	Derived from information in Shahar *et al*.
75+	1.41	1.40 to 1.42	Derived from information in Shahar *et al*.

TABLE 33 *Worsening heart failure hazard ratios used in the different submodels*

Device	HR	95% CI	Source
None (OPT)	Ref.	NA	Reference case
CRT-P	0.68	0.46 to 0.98	Clinical effectiveness, Chapter 3
CRT-D	0.68	0.46 to 0.98	Clinical effectiveness, Chapter 3
ICD	0.95	0.74 to 1.21	Lee *et al*.[124]

NA, not applicable.

TABLE 34 *Sudden cardiac mortality hazard ratios used in the different submodels*

Device	HR	95% CI	Source
None (OPT)	Ref.	NA	Reference case
CRT-P	0.75	0.45 to 1.18	Clinical effectiveness, Chapter 3
CRT-D	0.44	0.23 to 0.86	Clinical effectiveness, Chapter 3
ICD	0.37	0.27 to 0.50	Ezekowitz *et al*.[125]

NA, not applicable.

starting age. This was achieved by applying an age-dependent modifier to the probabilities derived from the survival curves for all forms of cardiac mortality in the OPT group.

The reference category for this was taken as 65–74 years to reflect the data in the systematic review. The figures for the age-dependent mortality HRs were derived from a US-based cohort study which had a reference case aged 35–64 years.[123] The revised HRs, which reflect the age-dependent HRs for all-cause mortality in the PenTAG model, are given in *Table 32*.

Death due to worsening heart failure

People with a CRT device can expect to experience a lower rate of mortality due to HF than those on OPT. These benefits are incorporated into the PenTAG model through HRs. Due to the large overlap of the CIs with both devices, we have combined the pooled values from *Figure 3* to produce the HRs for CRT-P and CRT-D in *Table 33*.

Lee and colleagues[124] reported that the RR of non-arrhythmic death in people with an ICD compared with OPT was 0.95, suggesting a slight benefit, although the 95% CI passes through one (*Table 33*).

Sudden cardiac death

People with either a CRT-D or an ICD are less likely to suffer from SCD than those on OPT. This benefit is represented in the PenTAG model through the use of HRs (*Table 34*).

In a recent systematic review/meta-analysis, Ezekowitz and colleagues[125] reported an HR of 0.37 (95% CI 0.27 to 0.50) for people with stand-alone ICDs compared with OPT (*Table 34*).

Derivation of post-transplantation mortality relative risk

The prognosis for people who receive a heart transplant is generally good. Hussey and colleagues[126] found that the median survival was 10.6 years and that 35% of people survived

TABLE 35 *Events used in the generation of transition probabilities in each of the submodels*

Event	Notes
Patient experiences a CRT-related infection	Possible in patient with a CRT device
Patient experiences an ICD-related infection	Possible in patients with an ICD device
Patient experiences a lead displacement	Possible in patient with either type of CRT device and also with ICD
Patient experiences a device replacement	Possible in patient with either type of CRT device and also with ICD
Arrhythmic event (VF, VT and syncopal VT)	Possible in all submodels
Surgical complications	Possible in people with CRT-P, CRT-D or ICD implants. Refers to a patient experiencing at least one adverse event as a result of the operation that can be corrected
Surgical failure	Possible in people who have any form of CRT implant. Refers to a patient experiencing at least one adverse event as a result of the operation that cannot be corrected
Perioperative death	Possible in people who have any form of re-surgery. Refers to death resulting from the operation in question
Hospitalisation due to HF	Possible in all submodels
Defibrillator upgrade post-HF hospitalisation	Possible in patients with either a CRT-P device or receiving OPT
Transplantation post-HF hospitalisation	Possible in all submodels following hospital admission

15 years postoperation. This contrasts strongly with the median survival of 3.7 years for people on OPT.

However, heart transplants are rare in the UK, with only around 300 performed per year.[126] Consequently, we were unable to identify any studies where either the RR or HR of deaths in people with transplants was measured against the general HF population. We have therefore crudely assumed that the RR in this group compared with those receiving OPT for HF is 3.7/10.6 = 0.35. The effect of changes in this parameter on the cost-effectiveness of each treatment is explored in the sensitivity analysis.

Event probabilities

At the chance nodes in the decision trees reproduced in Appendix 7, people in a particular model experience the events described in *Table 27* depending on probabilities. The values used for all event probabilities are also derived, where possible, from the literature and, where no information was available, from expert opinion. These are used to generate the transition probabilities in the submodels. *Table 35* contains a full list of event probabilities used in the construction of the PenTAG model.

Perioperative complications

Surgical complications

For the purposes of this report, adverse events are defined as those that result in death or permanent disability or require an invasive intervention to correct. Given the wide range of events that could happen, we have aggregated them into one health state based on pooled event probabilities from the included trials.

There is no clinical reason why people receiving a CRT-P device should experience a higher probability of perioperative complications than those receiving a CRT-D device. We have therefore made the assumption that the probability of a patient experiencing some form of complication is device independent. The pooled value used in the PenTAG model is presented in *Table 36*.

Initial implant failure and patient non-response

Although adverse events occur in (7%) and non-response (11–46%) in people receiving CRT (see Chapter 3), the model does not explicitly incorporate non-response (failure of left ventricular dyssynchrony to improve) and implant failure. As the data used to populate the model are largely drawn from trials using ITT, the effect of failed operations and patient non-response is implicitly incorporated into the event probabilities used in the model.

Survival data used to model sudden cardiac and worsening HF death are drawn from CARE-HF and the effect of failed operations and non-response is therefore incorporated into the mortality probabilities. Failed initial operations are also implicitly modelled, meaning that none of the

TABLE 36 *Event probabilities relating to surgical complications used in PenTAG cost-effectiveness model*

Parameter	Submodel	Value per 4-week cycle	Source
Patient experiences some form of perioperative complication	CRT-P	0.1063	Pooled average derived from CARE-HF,[71] MIRACLE[84]
	CRT-D	0.1063	CONTAK-CD[81]
	ICD	0.1063	And both treatment arms of COMPANION[75]

TABLE 37 *Event probabilities relating to perioperative death used in PenTAG cost-effectiveness model*

Parameter	Submodel	Value per 4-week cycle	Source
Patient dies following any form of operation in a particular cycle	CRT-P	0.0076	PenTAG systematic review, Chapter 3, *Table 22*
	CRT-D	0.0076	
	ICD	0.0076	

TABLE 38 *Event probabilities per cycle relating to lead infections*

Parameter	Submodel	Value per 4-week cycle	Source
Patient experiences an infection	CRT-P	0.0022	Derived from the numbers of events reported in MIRACLE, CONTAK-CD and CARE-HF, *Table 22*
	CRT-D	0.0022	
	ICD	0.0022	Assumed to be the same as CRT

original CRT-P or CRT-D cohorts enter the OPT submodel during the first cycle. However, during each subsequent cycle, if patients receive an invasive procedure, the possibility exists that it fails. *Table 22* shows that 9% of operations are classified as failures. Therefore, the cycle probability of failure used in the model for procedural failure is 0.0938.

The procedure to implant an ICD device is simpler than that to implant a CRT. We have therefore assumed that as long as a person survives the operation, the device is successfully implanted. Although this is a strong assumption, it is one that has been used in previous cost-effectiveness assessments of ICDs.[50]

Death

The probability of perioperative death has been used as the probability of death as a result of any operation in all three sub-models (*Table 37*).

Postoperative device-related events

Infection

This incorporates all infections related to the CRT devices and leads. Although a small minority of such infections can be dealt with using a course of antibiotics, the method generally used is to explant the device and leads, treat the infection, then re-implant a new device and leads.

There is no obvious clinical reason why a patient who has had a CRT-P device implanted should have a higher risk of infection than a patient who has had a CRT-D device implanted. We have therefore made the assumption that the event probability will be the same for both types of CRT device.

Given that the systematic review trials had differing follow-up durations, it was necessary to standardise the published results. The pooled event probability in *Table 38* was derived from these rates.

Due to a lack of data, we have assumed that the probability of an infection with an ICD device is the same as with a CRT device.

Lead displacement

Lead displacement was associated with the left ventricular lead. *Table 39* summarises the

TABLE 39 *Event probabilities per cycle relating to lead displacement*

Parameter	Submodel	Value per 4-week cycle	Source
Patient experiences a lead displacement	CRT-P	0.0015	Derived from expert clinical opinion
	CRT-D	0.0015	
	ICD	0.0000	Assumed zero as displacement is associated with the left lead

TABLE 40 *Intervals between device replacements*

Parameter	Submodel	Value (years)	Source
Patient receives a device replacement	CRT-P	6.5	Industry personal communication, expert opinion
	CRT-D	5.5	Industry personal communication, expert opinion
	ICD	5.0	Sanders *et al.*,[50] Medtronic personal communication

TABLE 41 *Event probabilities per cycle relating to arrhythmic events*

Parameter	Submodel	Value per 4-week cycle	Source
Patient experiences a major non-fatal arrhythmia requiring hospitalisation	OPT	0.0077	Derived from data in MIRACLE[84]
	CRT-P	0.0077	Derived from data in MIRACLE[84]
	CRT-D	0	It is assumed that the defibrillator responds successfully to all arrhythmic events
	ICD	0	It is assumed that the defibrillator responds successfully to all arrhythmic events

parameter values used in the PenTAG cost-effectiveness model.

Pulse generator replacement

In the PenTAG model, devices are modelled as surviving for a given period and then being automatically updated in all people who are alive at the end of the relevant period. From contact with device manufacturers and clinical experts, the mean service life of CRT-P devices was estimated as 6.5 years (5–8 years) and that of CRT-D to be 5.5 years (4–7 years). Note that this distribution is symmetrical, so no skew is being used to model a high demand in some patients.

Sanders and colleagues,[50] in their cost-effectiveness study of ICDs, reported that generators were replaced on average every 5 years (95% CI 2 to 9). The shorter lifetime of ICDs and CRT-D devices reflects the additional power requirements of the defibrillator. In people where the defibrillator is activated more frequently, the generator lifetime may be shorter.

Table 40 summarises the parameter values used to represent average device lifetime in the PenTAG cost-effectiveness model.

Arrhythmic event

We have defined a severe arrhythmic event as any occurrence of VF or syncopal VT. In the MIRACLE[88] study, over the mean follow-up time of 6 months there were 26 severe arrhythmic events in 532 people. This corresponds to an average arrhythmia rate of 10 events per 100 patient years. *Table 41* summarises the values used in the PenTAG cost-effectiveness model.

Hospitalisation due to heart failure

Hospitalisation in OPT group

Only CARE-HF,[71] COMPANION[75] and MIRACLE[6] report the number of hospitalisations reported in

TABLE 42 *Summary of hospitalisations due to heart failure in the main trials*

Trial	No. in OPT arm (*N*)	No. of events (*n*)	Follow-up period (months)	Event rate (per patient year)
CARE-HF	404	384	29.4	0.388
COMPANION	308	216	11.9	0.707
MIRACLE	225	50	6.0	0.503

TABLE 43 *Event probabilities per cycle for hospitalisation due to heart failure, trials evidence*

Parameter	Submodel	Value per 4-week cycle	Source
Patient is hospitalised as a result of HF	OPT	0.0381	Pooled estimate based on results drawn from CARE-HF, COMPANION, MIRACLE
	CRT-P	0.0249	Derived using RR from Chapter 3 and OPT probability
	CRT-D	0.0249	Derived using RR from Chapter 3 and OPT probability
	ICD	0.0381	Modeller assumption that risk is same as in the OPT subgroup

the control arms of the trials over their respective follow-up periods. This information is summarised in *Table 42*.

Using the numbers in each arm (*N*) as weights, the pooled yearly event rate is 0.505. From this value, the probability of an event in a given cycle can be calculated.

Hospitalisation for heart failure in CRT-P and CRT-D submodels

RRs for hospitalisation due to worsening HF, with each type of CRT device, relative to OPT were derived from the clinical systematic review (Chapter 3). The probability of hospitalisation for each CRT device can then be calculated by multiplying the OPT event probability (as derived from the yearly rate calculated above) by the relevant RR.

Hospitalisation for heart failure in ICD group

In the literature search, no studies were identified that contained information on hospitalisation rates in people with only an ICD. We have therefore made the assumption that people in this submodel have the same risk of hospitalisation as those in the OPT group (*Table 43*).

CRT-D upgrade after hospitalisation for heart failure

In the PenTAG model, people who are in the CRT-P or OPT submodels can receive upgrades to CRT-D or ICD devices, respectively, if they are hospitalised for HF with one or more of the following indications: (1) cardiac arrest due to either VT or VF, (2) spontaneous sustained VT causing syncope or significant haemodynamic compromise and (3) sustained VT without syncope or cardiac arrest.[44]

Data on the numbers of people that fall into this category are scarce. CARE-HF[71] reports that eight people in the CRT arm had a device with an additional defibrillator implanted during the follow-up period. The same study also reports that 23 people in the control group had an operation to implant a defibrillator. Assuming that these events happened posthospitalisation, then the probabilities of an upgrade occurring during each cycle are shown in *Table 44*.

Heart transplantation

MIRACLE[6] reports that of the 225 people in the control group, two received a transplant. This translates into a probability of 0.0014 of a patient receiving a transplant in a given cycle (1 month) if they had previously been in the hospitalisation due to HF state.

Resource use estimation

All resources used for the implantation and care of people with CRT devices were estimated for the PenTAG model.

For a summary of model parameters, values and sources see *Table 45*.

TABLE 44 *Event probabilities per cycle for defibrillator upgrades posthospitalisation due to heart failure*

Parameter	Submodel	Value per 4-week cycle	Source
Patient receives a defibrillator upgrade after being hospitalised due to heart failure	CRT-P	0.0005	CARE-HF[71]
	OPT	0.0015	CARE-HF[71]

TABLE 45 *Summary of the PenTAG model parameters, values and sources*

Parameter	Base case value	Rationale and source
Probability of death due to HF with OPT	Weibull distribution (λ 0.0027/γ 1.21)	Trial with UK patients, CARE-HF extension, Cleland (2006)[121]
RR of death due to HF with CRT	CRT-P/D HR 0.68 (95% CI 0.46 to 0.98)	PenTAG systematic review – pooled CRT-P and CRT-D
	ICD: HR 0.95 (95% CI 0.74 to 1.21)	Lee (2003)[124]
Probability of SCD with OPT	Weibull distribution (λ 0.0015/γ 1.29)	Trial with UK patients, CARE-HF extension, Cleland (2006)[121]
RR of SCD with CRT/ICD	CRT-P: HR 0.75 (95% CI 0.45 to 1.18) CRT-D: HR 0.44 (95% CI 0.23 to 0.86) ICD: HR 0.37 (95% CI 0.27 to 0.50)	PenTAG systematic review PenTAG systematic review Ezekowitz (2003)[125]
Probability[a] of hospitalisation due to HF with OPT	OPT: 0.0381	PenTAG systematic review
RR of hospitalisation due to HF with CRT/ICD	CRT-P/D: rate ratio 0.65 (95% CI 0.45 to 0.94) ICD: rate ratio 1.0	PenTAG systematic review – pooled CRT-P and CRT-D Assumed from pooled CRT-P + CRT-D
Probability[a] of a major arrhythmia requiring hospitalisation	OPT: 0.0077	MIRACLE-SR FDA report – assume CRT-P and OPT equivalent
	CRT-P: 0.0077	MIRACLE-SR FDA report – assume CRT-P and OPT equivalent
	CRT-D: 0	PenTAG model assumption
	ICD: 0	PenTAG model assumption
Probability of procedural failure	0.0938	PenTAG systematic review – pooled CRT-P and CRT-D
Probability[a] of perioperative complication CRT/ICD	0.1063	PenTAG systematic review – pooled CRT-P and CRT-D
Probability[a] of perioperative death CRT/ICD	0.0076	PenTAG systematic review – pooled CRT-P and CRT-D
Probability[a] of lead infection CRT/ICD	0.0022	PenTAG systematic review – pooled CRT-P and CRT-D
Probability[a] of lead displacement	CRT-P and -D: 0.015 ICD: 0.000	Derived from expert opinion PenTAG systematic review – pooled CRT-P and CRT-D
Probability[a] of upgrade to ICD post-HF hospitalisation	CRT 0.0005 OPT 0.002	CARE-HF, Cleland (2005)[71] CARE-HF, Cleland (2005)[71]
Need for transplant following HF hospitalisation	0.0014	MIRACLE
Device life in years	CRT-P: 6.5 CRT-D: 5.5 ICD: 5.0	Industry and expert consultation Industry and expert consultation Industry and expert consultation
Mean age in years	74.0	Mixed age cohort (35–84 years) reflects patients in UK practice, Cowie (1999)[12]

[a] Probability per model cycle (4-weeks).

TABLE 46 *Device costs of CRT systems, units and leads, and ICD systems and units (excluding value added tax)*

System components	CRT-P		CRT-D	
	N	Mean (£)	*N*	Mean (£)
Whole system cost (device with leads)	192	3,809	239	16,001
Unit cost (pulse generator unit only)	177	2,687	157	14,391
Leads[a]	443	359[a]	443	359[a]

N, no. of patient procedures.
[a] Assumed that leads used by CRT-P and CRT-D devices are the same or sufficiently similar to not affect price. NB: steroid-eluting leads appeared not to be priced very differently.
Source: Data supplied by NHS PASA on prices paid by 61 NHS 'buying units' during 2004 and 2005. Only device models where more than 10 were purchased (across all buying units) were included in calculating this cost estimate.

Implant of CRT devices

The cost of implanting a CRT device could be derived from the NHS National Schedule of Reference Costs (NSRC, 2005) either for Pacemaker Implant for AMI, Heart Failure or Shock (HRG = E07) or Pacemaker Implant **except** for AMI, Heart Failure or Shock (HRG = E08). However, it is believed (based on our clinical experts' opinions) that the cost of implanting a CRT device (either CRT-P or CRT-D) is probably greater than implanting other types of pacer, mainly because of the greater time required to place the left ventricular lead (from an extra 15 to 90 minutes). Also, the NSRC HRG costs do not distinguish the staff and catheter laboratory equipment costs of surgical implantation from the cost of the devices themselves – which for CRT units and leads can be considerable.

We therefore obtained accurate device costs paid by NHS Trusts from the NHS Purchasing and Supplies Agency (PASA, personal communication) (*Table 46*). These are the actual prices paid, excluding value added tax, by a sample of 61 NHS 'buying units' (either individual NHS Trusts or purchasing consortia of NHS Trusts) during 2004 and 2005.

The surgical procedures for implanting a CRT-P and a CRT-D device are essentially the same, so we have assumed that any difference in the cost of implanting each type of device will be the difference in the cost of the devices themselves.

In addition to the CRT device cost, we have added a cost of £1265 for the mean total cost of cardiac catheter laboratory staff time, consumables and (annualised) capital equipment cost and immediate preoperative and postoperative care. In the absence of other reliable sources, this estimate is based on a recent budget impact analysis for NHS Scotland (coronary heart disease) of the non-device costs of CRT implantation. The data from that document are summarised in *Table 47*.

Implant or revision of ICD device

There is also a choice between several HRGs for the implantation or replacement/revision of an ICD device (*Tables 48* and *49*). These data are consistent with cost data supplied to us by the NHS PASA which show that the mean price paid in 2004 and 2005 by NHS Trusts for ICD systems (with required leads) and ICD units (without leads) was £11,098 and £11,028, respectively. We have used the NSRC 2005 elective hospital admission cost for defibrillator implant and explant (HRGs E08SD and E08SD).

Cost of managing device-related problems

The three most common device-related problems of lead displacement/failure, lead infection and battery replacement/failure typically require different management approaches. These may require replacement of the device itself, the leads or both the device and leads. On the basis of independent views from two of our expert clinical advisors, *Table 50* shows our main assumptions regarding the resource consequences of each CRT problem.

Lead displacement/failure

Lead displacement or failure requires an operation to adjust or replace the lead, but will not usually require the replacement of the CRT device itself. For consistency, we assume the same operation cost as assumed in the implantation cost (£2000) plus the cost of one new lead (£359). Therefore, the mean cost of treating lead displacement/failure is £2359.

TABLE 47 *Estimated non-device CRT implantation costs (NHS Scotland, 2005)*

Activity/resources	Best (£)	Lower (£)	Higher (£)	Notes
Preoperative care and tests	428	NS	NS	Staff and test (ECHO and chest X-ray) costs plus overhead
Procedure: direct staff costs	410	400	430	Average of 1.5 CRTs implanted per session (in a 10-session week in a cardiac catheter laboratory)
Procedure: capital costs	267	200	370	Annualised, and based on an assumed current cost of a completely equipped catheter laboratory of £1million, and adding 5% annual maintenance costs (assumed)
Procedure: consumables	100	NS	NS	Source not stated
Immediate postoperative care, device programming and tests	60	NS	NS	45 minutes of an MTO 4 grade cardiac technician (£32 per hour)[a], with a consultant cardiologist in 10% of cases (£88 per patient-related hour; Unit Costs of Health and Social Care, 2005), plus chest X-ray (£19; NSRC, 2005, radiology Band A test)
Total estimated non-device cost of CRT implantation	1265	1188	1388	

NS, not stated in source document.
[a] MTO 4 grade technician, assumed to be paid at the mid-point of Agenda for Change pay band 7 (from 1 April 2005 = annual gross salary of £31,127).

TABLE 48 *Estimated non-device ICD implantation costs (NHS Scotland, 2005)*

Activity/resources	Best (£)	Lower (£)	Higher (£)	Notes
Preoperative care and tests	0	NS	NS	These tests are likely to have been incurred as part of their standard medical treatment for arrhythmia
Procedure: direct staff costs	205	200	215	Average of 3 ICDs implanted per session (in a 10-session week in a cardiac catheter laboratory)
Procedure: capital costs	133	100	185	Annualised, and based on an assumed current cost of a completely equipped catheter laboratory of £1million, and adding 5% annual maintenance costs (assumed)
Procedure: consumables	100	NS	NS	Source not stated
Immediate postoperative care, device programming and tests	60	NS	NS	20 minutes of an MTO 4 grade cardiac technician (£32 per hour)[a], with a consultant cardiologist in 10% of cases (£88 per patient-related hour; Unit Costs of Health and Social Care, 2005), plus chest X-ray (£19; NSRC, 2005, radiology Band A test)
Total estimated non-device cost of ICD implantation	498	460	560	

NS, not stated in source document.
[a] MTO 4 grade technician, assumed to be paid at the mid-point of Agenda for Change pay band 7 (from 1 April 2005 = annual gross salary of £31,127).

TABLE 49 *NHS NSRC average unit costs for implanting ICDs*

HRG	HRG description		No. of FCEs	Average length of stay (days)	2005 national average unit cost (£)
E08SD	Pacemaker implant except for AMI, heart failure or shock – defibrillator implant and explant only	Elective	693	2.8	15,187
		Non-elective	936	4.6	11,812
E09SD	Pacemaker replacement/revision except for AMI, heart failure or shock – defibrillator implant and explant only	Elective	295	2.6	16,103
		Non-elective	164	5.0	10,993

FCE, finished consultant episodes.
Source: National Schedule of Reference Costs, 2005, for NHS Trusts.

TABLE 50 *Resource consequences of different device problems*

Device problem type	Replace device?	Replace lead(s)?	Hospital admissions?	Other resources?
Lead displacement/failure	No (not usually)	Yes – 1 or 2	One admission – approximately the same as original implant procedure (24 hours)	
Lead infection	Yes	Yes – all	Two admissions – one to explant device and treat infection (often 7–10 days); one to implant new device after infection has cleared	I.v. antibiotics Outpatient visit(s) to check absence of infection
Battery replacement/failure	Yes	No (not usually)	One short admission	

Lead infection

Lead infection typically requires (1) a hospital admission for an operation to explant the device and its leads, (2) a prolonged (7–10-day) hospital stay to control the infection, (3) postdischarge outpatient visits to confirm absence of infection and (4) implantation of a new device and leads.

For the hospital stay to explant the CRT device and treat the infection we have used the NHS NSRC cost for explanting a pacemaker in patients who are over 69 years old and/or have concomitant co-morbidities (HRG: E09, Non-elective, which has a mean length of stay of 4 days), £2785, plus the cost of three extra bed-days for this HRG (£299 per day).

Battery replacement/failure

Since the batteries are integral to the pulse generator units (in CRT and ICD devices), this involves replacement of the device itself. The catheter laboratory staff, consumables and equipment usage cost is assumed to be the same as for any other pacemaker replacement (source: expert advisers). However, the CRT or ICD device leads would not normally be replaced, in particular the left ventricle lead for CRT devices.

Cost of managing ICD device problems

We assume that ICDs result in the same types of device-related problem as CRT devices, that is, lead displacement/failure, lead infection and battery failure. The cost of managing each of these problems is shown in *Table 51* and assumes the same approach to clinical management as for CRT devices.

Summary of device implantation costs and device-related complication costs

Table 52 summarises our calculation of device implantation costs and costs associated with managing device-related complications of ICDs and CRT systems.

Resource use and cost of states associated with hospitalisation

Hospitalisation for heart failure

The NHS NSRC provides a number of estimates of the cost of hospitalisation for HF, depending on whether admissions are elective or non-elective,

TABLE 51 *Ingredient costs included in calculation of cost of treating lead infections*

Resource or event	Base case (£)	Lower value (£)	Upper value (£)	Source and justification
Surgical admission to explant CRT-P, CRT-D or ICD system (both pulse generator unit and leads) (mean length of stay: 4 days)	2,785	1,154	3,243	NSRC estimates for non-elective cardiac Pacemaker Replacement/Revision: HRG E09. Upper and lower values also from NSRC HRG E09
Extra 3 bed-days[a] or 6 bed-days[b]	897[a]	543[a]	2,190[b]	NSRC estimates for excess bed-day costs for HRG E09. Mean unit cost per bed-day, £299; lower quartile, £181; upper quartile, £365
Outpatient appointment to confirm absence of infection	97	73	115	NSRC 2005, for HRG E18 (elective)
Re-implantation of new CRT-P system	5,074	4,997	5,197	As for first implant (cost mainly comprises device costs and time to place left ventricular lead)
Re-implantation of new CRT-D system	17,226	17,189	17,389	As for first implant (cost mainly comprises device costs and time to place left ventricular lead)
Re-implantation of new ICD system	11,596	11,558	11,658	NSRC, 2005, for HRG E09DF (elective)
Total cost of treating lead infection with CRT-P	8,853	6,767	10745	Sum of relevant device explantation, extended hospital admission, outpatient costs and device re-implantation costs (above)
Total cost of treating lead infection with CRT-D	21,045	18,959	22,937	Sum of relevant device explantation, extended hospital admission, outpatient costs and device re-implantation costs (above)
Total cost of treating lead infection with ICD	15,375	13,328	17,206	Sum of relevant device explantation, extended hospital admission, outpatient costs and device re-implantation costs (above)

TABLE 52 *Summary of costs of device implantation and treating device-related complications*

	Implantation of a new CRT or ICD system (unit with leads)						
		Procedure cost (£)[a]			Total treatment cost (£)		
	Item (£)	Base case	Lower	Higher	Base case	Lower	Higher
System							
	System						
CRT-P	3,809	1,265	1,188	1,388	5,074	4,997	5,197
CRT-D	16,001	1,265	1,188	1,388	17,266	17,189	17,389
ICD	11,098	498	460	560	11,596	11,558	11,658
Lead displacement/replacement							
	Lead						
CRT-P	359	1,265	1,188	1,388	1,624	1,547	1,747
CRT-D	359	1,265	1,188	1,388	1,624	1,547	1,747
ICD	359	498	460	560	857	819	919
Battery failure/replacement							
	Unit						
CRT-P	2,687	633	594	694	3,320	3,281	3,381
CRT-D	14,391	633	594	694	15,024	14,985	15,085
ICD	11,028	498	460	560	11,526	11,488	11,588

[a] Procedure costs include the cost of preoperative care and tests, direct staff costs, annualised cost of capital equipment, consumables and postoperative care and tests (including programming of device). See *Tables 47* and *48*.

Sources: NHS PASA (data supplied on cost of systems, units and leads); NHS Scotland report on budget impact of ICDs and CRTs (procedure costs – see footnote above).

TABLE 53 *Costing assumptions about the prevalence of drug usage (by NYHA class), typical daily dose and drug brand*

Drug	Proportion of CRT-eligible HF patients, by NYHA class (%)				Drug brand and assumed mean dose (mg/day)		
	I	II	III	IV	Base case	Lower	Upper
ACE or angiotensin II	95	95	95	95	Ramipril 10	Ramipril 10	Perindopril 4
Diuretics	0	0	20	50	Bendro flumethazide 2.5	Bendro flumethazide 2.5	Bendro flumethazide 2.5
β-Blockers	20	20	50	65	Carvedilol 50	Bisoprolol 10	Carvedilol 50
Aldosterone antagonist	0	0	30	50	Spironolactone 25	Spironolactone 25	Spironolactone 25
Digoxin	5	10	35	45	Dogoxin 0.25	Dogoxin 0.25	Dogoxin 0.25
High-dose loop diuretic	10	10	60	90	Frusemide 100	Frusemide 100	Bumetonide 2

Source: information supplied by two consultant cardiologists working in the NHS (using interpolation where estimates differed).

and whether the person is aged 70 years or over, or has co-morbidities. We asked our expert clinical advisers whether they thought the costs of hospitalisations for HF in people with a pre-existing diagnosis of HF and with a CRT device would be different from the cost of hospitalisation for HF in general. Overall, for CRT patients, our experts believed that their hospital admissions would be less costly because (1) their condition will be better known and already controlled and (2) interrogation or re-programming of the device may result in more rapid resolution of the problem.

In the absence of reliable evidence to inform how much less costly these hospital admissions would be, our reference case analysis uses the lowest of the available costs for this HRG (NSRC cost for non-elective finished consultant episodes, HRG E19 (Heart Failure or Shock, in those <70 years old or without concomitant co-morbidities), £1298, and the related lower and upper quartile estimates.

Hospitalisation for arrhythmia

The NHS NSRC provides a number of estimates of the cost of hospitalisation for arrhythmias. As for hospitalisations due to HF we used the lowest of the available costs (NSRC cost for non-elective finished consultant episodes HRG E19 (Heart Failure or Shock, in those <70 years old or without concomitant co-morbidities), £606, and associated lower and upper quartile estimates.

Resource use

Levels of resource use in each model arm are determined by state-transition probabilities and event rates.

Discount rates

Benefits and costs are both discounted using an annual rate of 3.5% in accordance with UK Treasury guidelines.[116]

Cost of optimal pharmacological therapy

People on OPT only and those with CRT devices take a range of drugs for HF. In order to estimate the cost of these drugs, we have made some simplifying assumptions about the proportions of people in different NYHA classes taking different classes of drugs, and the exact formulation and mean daily dose taken. These assumptions were informed by detailed responses from two of our expert clinical advisers (consultant cardiologists in the NHS), and are summarised in *Table 53*.

The proportions for NYHA class II and IV, and the range of drug classes, are broadly similar to those recorded at baseline in the CARE-HF and COMPANION trials.

The costs per 4-week cycle are shown in the summary table of unit costs (*Table 54*). Even for HF patients in NYHA class IV, the 4-weekly cost of OPT is estimated to be between only £9 and £22. The 4-weekly cost of OPT for NYHA class I patients only reduces to between £3 and £12.

TABLE 54 *Summary of unit costs used in the model including source and justification*

Procedure	Base case (£)	Lower value (£)	Upper value (£)	Source and Justification
Surgery to implant new CRT-P system (pulse generator unit and required leads)	5,074	4,997	5,197	NHS PASA (system cost) plus £1,265 (£1,188–1,388) cost of implantation procedure
Surgery to implant new CRT-D system (pulse generator unit and required leads)	17,266	17,197	17,389	NHS PASA (system cost) plus assumed £1,265 (£1,188–1,388) cost of implantation procedure
Surgery to implant a new ICD system (unit plus leads)	11,596	11,558	11,658	NHS PASA (system cost) plus assumed £498 (£460–560) cost of implantation procedure
Treatment of infection (including CRT-P explant and implant of new CRT-P after clearance of infection)	8,853	6,767	10,475	NSRC 2005,[56] cost for pacer explant, plus cost of 3 extra hospital bed-days to treat infection, plus cost for replacement of CRT-P
Treatment of infection (including CRT-D explant and implant of new CRT-D after clearance of infection)	21,045	18,959	22,937	NSRC 2005,[56] cost for pacer explant, plus cost of 3 extra hospital bed-days to treat infection, plus cost for replacement of CRT-D
Treatment of ICD infection (including ICD explant and implant of new ICD after clearance of infection)	15,375	13,328	17,206	NSRC 2005,[56] cost for pacer explant, plus cost of 3 extra hospital bed-days to treat infection, plus cost for replacement of ICD
Treatment of lead displacement/ failure (with CRT-P or CRT-D)	1,624	1,547	1,747	NHS PASA cost of one new lead, plus assumed £1,265 (£1,188–1,388) cost of procedure (i.e. same as new system implant because most of the procedure time is due to positioning of left ventricular lead)
Treatment of ICD lead displacement/failure	857	819	919	NHS PASA cost of one new lead, plus assumed £498 (£460–560) cost of procedure (i.e. same as new system implant)
CRT-P battery/unit replacement (including replacement with new CRT-P unit)	3,320	3,281	3,381	NHS PASA (cost of pulse generator unit) plus assumed £633 procedure cost. Upper and lower values are estimated using NSRC 2005 interquartile range for elective pacemaker replacement/revision (HRG: E09)
CRT-D battery/unit replacement (including replacement with new CRT-D unit)	15,024	14,985	15,085	NHS PASA (cost of pulse generator unit) plus assumed £633 procedure cost. Upper and lower values are estimated using NSRC 2005[56] interquartile range for elective pacemaker replacement/revision (HRG: E09)
Battery/unit replacement of an ICD unit	11,526	11,488	11,588	NHS PASA (system cost) plus assumed £498 (£460–560) cost of implantation procedure
Heart transplant	34,024	14,525	40,150	NSRC 2005,[56] for HRG E02 (weighted average of average unit cost of elective and non-elective finished consultant episodes)
Non-elective hospitalisation for heart failure	1,298*	932*	2,579**	NSRC 2005,[56] for HRGs E19* and E18**
Non-elective hospitalisation for arrhythmia	606*	443*	1,656**	NSRC 2005,[56] for HRGs E30* and E29**
Outpatient cardiology specialist follow-up appointment (6-monthly)	97	73	115	NSRC 2005[56] (Table for Output Appointments Follow Up Adults table)

continued

TABLE 54 *Summary of unit costs used in the model including source and justification (cont'd)*

Procedure	Base case (£)	Lower value (£)	Upper value (£)	Source and Justification
4-weekly cost of OPT drugs for HF NYHA class I	5	3	12	BNF 51[118] costs of ACE/angiotensin II inhibitors, β-blockers, aldesterone antagonists, digoxin, diuretics and high-dose loop diuretics at daily typical doses
4-weekly cost of OPT drugs for HF NYHA class II	5	3	12	BNF 51[118] costs of ACE/angiotensin II inhibitors, β-blockers, aldesterone antagonists, digoxin, diuretics and high-dose loop diuretics at daily typical doses
4-weekly cost of OPT drugs for HF NYHA class III	11	7	18	BNF 51[118] costs of ACE/angiotensin II inhibitors, β-blockers, digoxin and high-dose loop diuretics at daily typical doses
4-weekly cost of OPT drugs for HF NYHA class IV	15	9	22	BNF 51[118] costs of ACE/angiotensin II inhibitors, β-blockers, digoxin and high-dose loop diuretics at daily typical doses

TABLE 55 *Proportion of survivors in CARE-HF trial in each NYHA class*

NYHA class	At baseline (%)[a]: OPT and CRT	At 90 days (%)[b]		At 18 months (%)[c]	
		OPT	CRT	OPT	CRT
I	0	10.1	29.5	12.7	31.5
II	0	29.9	41.5	37.3	44.4
I or II	0	40.0	71.0	50.0	75.9
III	93.8	54.8	27.2	45.7	22.5
IV	6.2	5.2	1.8	4.3	1.5

[a] As reported in Table 1 of Cleland *et al*., 2005.
[b] Proportion in NYHA class I or II from Cleland PowerPoint presentation of CARE-HF results (accessed on 7 August 2006); proportion of these figures in classes I, II and III, IV derived from the 18-month data (Figure 13 in joint industry submission).
[c] Read from bar chart (Figure 13 in joint industry submission).

Compared with the cost of implanting CRT devices, or managing device-related problems, these costs are therefore very small indeed, so we believe that our simple cost assumptions relating to OPT are justified.

Resource use

Levels of resource use in each model arm are determined by the state-transition probabilities and event rates and probabilities already described earlier.

In addition, the proportions of surviving people in each arm in each NYHA class (which determines both OPT costs and utility weights) were taken from the CARE-HF trial results (*Table 55*). Straight-line interpolation was used to estimate the proportions in each NYHA class (cycles 2–3 and 5–20), and the NYHA class mix of patients after 18 months was assumed to stay the same.

Utilities associated with CRT for heart failure

Utilities by NYHA subclass

In addition to increased survival, the main clinical benefits of CRT appear to include an improvement in health-related QoL. Most modelling-based economic evaluations have accordingly incorporated changes in QoL, typically by stratifying their simulated patients by NYHA class of HF severity, and then attaching a utility weight to people in each NYHA class.[111,112,114]

Although we have chosen not to reflect different NYHA classes in the structure of our decision model (for the reasons already stated; see the

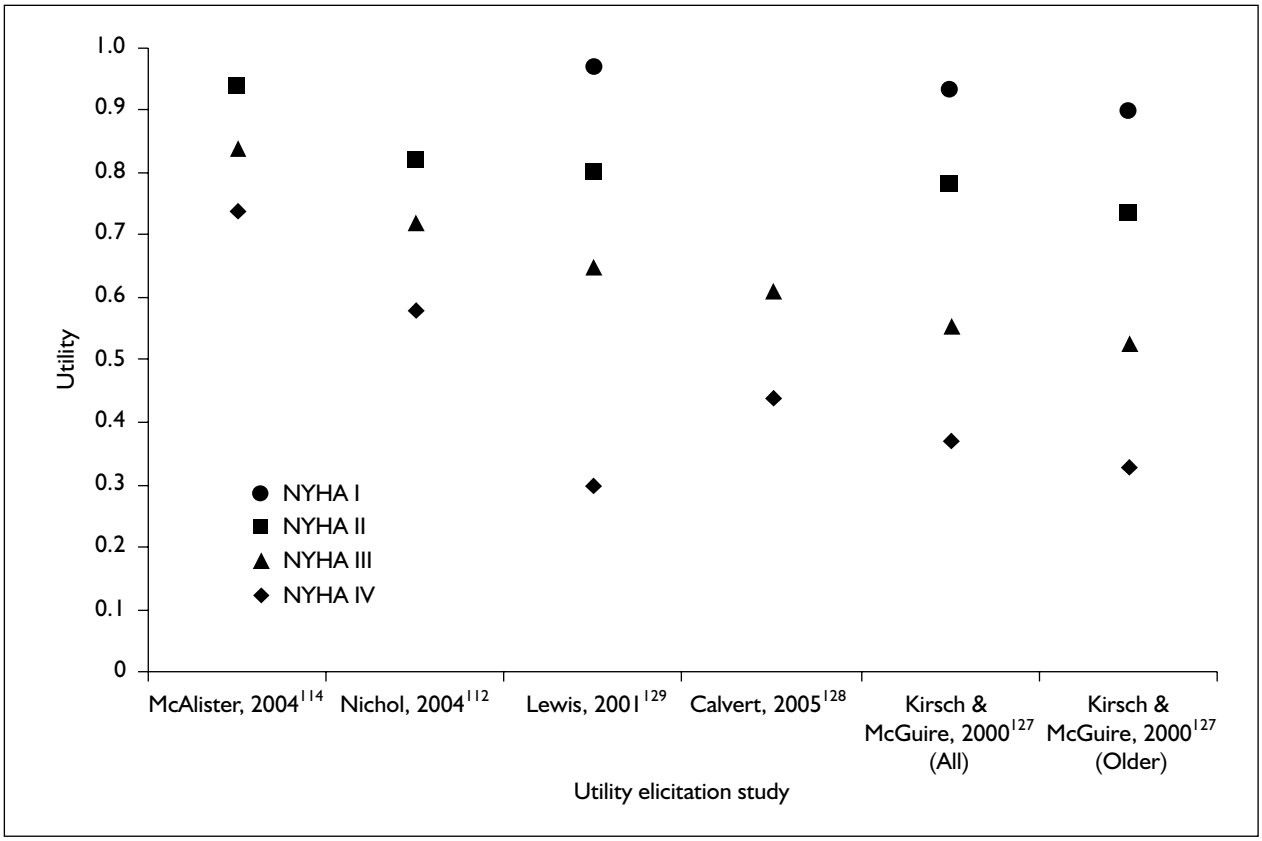

FIGURE 18 *Published utility estimates for living with different severities of heart failure. Note that the utility estimates from Nichol and colleagues are those reported in the online appendix that describes their methods for assessing health-related QoL.[112] They differ from those reported in the full paper (which are the same as those used by McAlister and colleagues[114]).*

section 'Methods', p. 41), we still need to rely on NYHA-specific estimates of health-related QoL to derive time-dependent utility estimates for our model.

Figure 18 shows the utility estimates from published studies which have elicited utilities for the different NYHA classes of HF. Of these studies, two used the standard gamble technique amongst a sample of older adults in the USA, using health state descriptions developed by cardiologists from Health Utilities Index descriptors (McAlister and colleagues,[114] $n = 90$; Nichol and colleagues,[112] $n = 66$). A study by Kirsch and McGuire,[127] with a focus that was primarily methodological, used the time trade-off technique with a representative sample of 64 members of the British public to derive NYHA class-specific utility estimates.

The CARE-HF trial used the EQ-5D instrument at baseline and at 90 days, and social preference weights for this instrument for the UK population are available.[108,128] The baseline estimate for all CARE-HF trial participants was 0.6 (95% CI 0.58 to 0.62), and the mean EQ-5D utility score for NYHA class III participants was 0.17 greater than for NYHA class IV participants; therefore, the NYHA class III- and IV-specific utility values can be calculated (and are 0.61 and 0.44, respectively).[128] Finally, for our purposes, the utility estimates produced by Lewis and colleagues[129] should be disregarded as they were derived from a sample of people with advanced HF (rather than a sample of the general public, which is the preferred source of health state preferences for technology appraisals for NICE). It is worth noting that the difference in utility between NYHA class IV and class II varies considerably across these studies (from 0.50 to 0.20; see *Figure 18*).

Other studies have developed regression-based algorithms for translating the scores of the MLWHF questionnaire into utilities (e.g. Havranek and colleagues,[115] Calvert and colleagues[128] based on CARE-HF trial data). However, the correlation between the measured utilities and the MLWHF score was very weak (r^2 = only 0.1 for the curvilinear equation derived by Havranek and colleagues).

TABLE 56 *Utility values used in the decision model with their source*

Severity of HF	Base case	Lower estimate	Higher estimate	Source
NYHA class IV	0.44	0.421	0.461	Calvert *et al.*[128]
NYHA class III	0.61	0.591	0.631	Calvert *et al.*[128]
NYHA class II	0.78	0.722	0.842	Kirsch and McGuire[127]
NYHA class I	0.93	0.912	0.960	Kirsch and McGuire[127]
Hospitalisation with HF	0.57	0.480	0.800	McAllister *et al.*[114]

TABLE 57 *Proportion of survivors in the CARE-HF trial who were in each NYHA class, by trial arm and time point*

NYHA class	At baseline (%):[a] OPT and CRT	At 90 days (%)[b]		At 18 months (%)[c]	
		OPT	CRT	OPT	CRT
I	0	10.1	29.5	12.7	31.5
II	0	29.9	41.5	37.3	44.4
I or II	0	40.0	71.0	50.0	75.9
III	93.8	54.8	27.2	45.7	22.5
IV	6.2	5.2	1.8	4.3	1.5

[a] As reported in Table 1 of Cleland *et al*., 2005.
[b] Proportion in NYHA class I or II from Cleland PowerPoint presentation of CARE-HF results (accessed on 7 August 2006); proportion of these figures in classes I, II, and III, IV derived from the 18-month data (Figure 13 in joint industry submission).
[c] Read from bar chart (Figure 13 in joint industry submission).

Since Calvert and colleagues[128] endorse the use of the EQ-5D as a valid measure of health-related QoL in this patient group, and there are also UK-based social preference weights for the EQ-5D, we used their values for NYHA class III and IV. For NYHA class I and II we used the values derived by Kirsch and McGuire[127] since they also use a choice-based method amongst a representative sample of the UK population. We would have preferred to obtain all our utility estimates from the same study, but the best source, the CARE-HF study, did not report utility weights for those in NYHA class I and II. In contrast, the Kirsch and McGuire study does estimate utilities for all four NYHA classes and is UK-based, but the estimates are from a small sample and the quantification of QoL effects did not use a standardised and validated generic instrument (e.g. EQ-5D). In any case, the utility values for NYHA class III and IV are fairly similar between these two studies.

Finally, the study by McAlister and colleagues[114] is the only one to have derived a utility weight for a description of "congestive heart failure severe enough to require hospitalisation" (utility = 0.57; low 0.48 to high 0.80). We used this value in our model to calculate the utility of hospitalisation due to HF (assuming that 1 week of the 4-week model cycle is spent at this level of utility) (*Table 56*).

These NYHA class-specific utilities were then combined using the distribution of subjects by NYHA class from the CARE-HF trial (at baseline, 90 days and 18 months). The data points in *Table 57* were used to generate cycle-specific mean utilities for each comparator arm in the model (using straight-line interpolation where necessary). In the base case analysis, people surviving beyond 18 months were assumed to retain the mix of NYHA class of survivors at 18 months.

Chapter 5
Results

Cost-effectiveness of CRT-P compared with OPT

Base case results for cost-effectiveness

Base case results produced by the economic model for different cohort starting ages and also for the overall mixed age cohort are shown in *Table 58* on a per patient basis. For the mixed age cohort, in comparison with OPT the implantation of a CRT-P device provides an extra 0.70 QALYs (254 quality-adjusted days). This improvement would cost the NHS £11,630 per patient to achieve. There is some evidence of heterogeneity between age groups.

Model outputs and model validation

Event counts

During each cycle, people may experience any of the events listed in *Table 59*. The numbers of each of these events occurring in both treatment and comparator arms of the model can be aggregated over the whole time horizon to provide useful comparative outputs, and also a validation tool against clinical data and experience. The event counts produced in the CRT-P and OPT arms of the model are shown in *Table 59*. With the exception of the expected number of HF hospitalisations, values are presented as the probability that an individual patient will experience the particular event during their remaining life. In this instance, a person's remaining life is taken to mean the amount of time alive from the start of the model (postimplantation).

The model predicts a 22.7% relative reduction in the number of hospitalisations due to worsening HF over the average person's remaining life in people with a CRT-P device implanted compared with people receiving OPT. People receiving OPT can expect to experience 2.4 hospitalisations over their remaining life. As the mean expected lifetime for people in this group is 4.9 years, people with devices can expect to be hospitalised on average every 2.1 years (0.48 events per year). The corresponding rate for patients with a CRT-P device is 1.8 events over their remaining lifetime. Given that the mean lifetime for patients with a CRT-P device is 5.8 years, this corresponds to individuals being hospitalised on average every 3.2 years (0.32 events per year).

The annual rate produced by the PenTAG model for patients on OPT is similar to values presented in the literature. Khand and colleagues,[52] in a long-term cohort study of 9718 people who had previously been admitted to hospital for HF, reported that over a 3-year period the rate of readmission was 1.8 per person. This corresponds to a crude rate of 0.6 events per patient year. Interestingly, if median rather than mean survival is used to calculate yearly event rates, the model produces a figure much closer to that of Khand and colleagues (expected median survival 3.77 years, hospitalisation rate 0.63 events per year).

Survival

Table 60 summarises age-related model outputs relevant to expected lifetimes of patients in the

TABLE 58 *Discounted base case cost-effectiveness results per patient for CRT-P compared with OPT (lifetime time horizon), by age and mixed age cohort*

Start age (years)	OPT costs (£)	OPT QALYs	CRT-P costs (£)	CRT-P QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
30	17,673	5.52	34,861	6.70	17,188	1.17	14,630
40	17,422	5.45	34,320	6.59	16,898	1.14	14,843
50	16,601	5.22	32,716	6.27	16,116	1.04	15,374
60	13,863	4.44	28,180	5.33	14,317	0.89	16,073
70	10,030	3.31	22,212	4.07	12,182	0.76	16,027
80	7,422	2.52	17,872	3.13	10,448	0.61	17,143
90	5,933	2.07	15,178	2.53	9,245	0.46	20,333
Mixed	**9,367**	**3.10**	**20,997**	**3.80**	**11,630**	**0.70**	**16,735**

TABLE 59 *Patient-relevant outcomes in the economic model for mixed age cohorts of 1000 people*

	OPT + upgrades (%)		CRT-P + upgrades[a] (%)		Difference (%)
	Event likelihood over lifetime	Event rate per 100 patient-years	Event likelihood over lifetime	Event rate per 100 patient-years	
Lead infection	4.5	0.93	15.3	2.89	+10.8
Lead displacement	0	0.00	10.3	1.89	+10.3
Routine device change	28.7	NA	49.3	NA	+20.6
CRT-P	0	NA	19.3	NA	NA
CRT-D	0	NA	28.5	NA	NA
ICD	28.7	NA	1.5	NA	–27.2
Device upgrades	32.0	NA	37.4	NA	+5.4
CRT-D	0	NA	35.9	NA	NA
ICD	32.0	NA	1.6	NA	–30.4
Serious arrhythmic event	32.0	7.82	37.4	8.16	+5.4
Surgical complication	6.9	1.45	21.9	4.29	+15.0
Surgical failures	0	NA	5.8	1.03	NA
Heart transplant	0.3	0.06	0.3	0.04	0
No. of hospitalisations as a result of HF	2.36	47.9	1.82	31.7	–0.54

NA, not applicable.
[a] An upgrade from OPT can be to ICD and from CRT-P to CRT-D or ICD.

TABLE 60 *Survival outputs for people in OPT and CRT-P arms, by age and mixed age cohort*

Start age (years)	Median survival OPT (years)	Mean survival OPT (years)	Median survival CRT-P (years)	Mean survival CRT-P (years)
30	7.31	9.7	9.08	11.6
40	7.23	9.5	9.00	11.2
50	7.15	8.9	8.77	10.4
60	6.15	7.3	7.15	8.4
70	4.46	5.2	5.39	6.1
80	3.08	3.9	3.77	4.6
90	2.31	3.2	2.69	3.7
Mixed	**3.77**	**4.9**	**4.62**	**5.8**

TABLE 61 *Additional life for people in CRT-P arm compared with OPT arm*

Start age (years)	25% centile (years)	Median survival (years)	75% centile (years)	Mean survival (years)	Proportional increase in overall median survival (%)
30	0.85	1.77	2.85	1.9	24.2
40	0.92	1.77	2.77	1.8	24.4
50	0.85	1.62	2.39	1.5	22.6
60	0.77	1.00	1.69	1.1	16.3
70	0.54	0.92	1.15	0.9	20.7
80	0.31	0.69	0.92	0.7	22.5
90	0.15	0.39	0.69	0.5	16.7
Mixed	**0.39**	**0.85**	**1.08**	**0.9**	**22.4**

OPT and CRT-P cohorts. *Table 61* shows age-dependent survival gains for CRT-P compared with OPT. In the general population of people with HF, a majority of people will die within a particular period and a few will live a long time. This means that the distribution of people's remaining lives will be skewed. For that reason, both median and mean survival have been included in all tables.

Table 61 shows that people with a CRT device can, on average, expect to live over 9.5 months longer (0.8 of a year) than people on OPT.

The overall trial-based pooled RR reduction for all-cause mortality for CRT-P versus OPT was 0.68 (95% CI 0.54 to 0.88). The model outputs show a similar result for the population-based analysis [RR reduction 0.84, 95% credibility interval (CrI) 0.83 to 0.85].

In the PenTAG model, mortality is incorporated through survival curves. However, people in the OPT arm experience non-cardiac and age-related mortality risk and so it is necessary to validate the survival percentages produced against other published data.

The Framingham heart study gave data on 1- and 5-year age-adjusted mortality for men and women.[130] We compared these with our data; after adjusting the separate values their 1- and 5-year mortality figures are 17.2% (95% CI 8.3 to 25.64%) and 48.9% (95% CI 28.7 to 58.96%), respectively. The corresponding 1- and 5-year mortality figures produced by the PenTAG model for a simulated cohort of 70-year-olds are 10.93 and 53.99%, respectively. Both of these values lie within the CIs generated from Levy and colleagues.[130]

There is a paucity of data for validation of model outputs. Only CARE-HF had a follow-up long enough to allow 25% of people to die. The 25th centile for all-cause mortality in the CRT group was approximately 3.2 years.[74] The interquartile range (IQR) of participants' ages in the trial was 60 to 73 years and this value represents the average value across all participants. The 25% mortality value produced by the PenTAG model when the starting age was set to 65 years was 2.62 years, although there is significant age-dependent variation (start age 60 years expected 25% survival 4.1 years; start age 73 years expected 25% survival 2.4 years). Without knowing the age distribution of people in the CARE-HF trial, it is hard to know how to weight these outputs in order to make a direct comparison. However, the model does appear to be producing values for overall survival that are broadly similar to those reported in CARE-HF.

State occupancy

State occupancy shows how long people spend in each of the modelled health states. For the purposes of presentation, occupancy values for each state (e.g. lead displacement) in each of the submodels are combined to produce one overall value. The mean state occupancies, over the time horizon of the model, for each of the CRT-P and OPT arms of the model are presented in *Table 62*.

Clearly, people in both arms of the model spend most of their expected average remaining life in the 'stable' meta-state. The only other state where people spend any significant amount of time alive is 'HF hospitalisation'. People on OPT spend more time in that meta-state than people with a CRT device.

Sensitivity analysis

The ICER is the ratio of the incremental cost of treatment and the incremental benefits of treatment (i.e. difference in costs/difference in QALYs) between two interventions. Although this

TABLE 62 *Overall state occupancies per person in the model for mixed age cohorts of 1000 people (excluding all death states)*

State	OPT + upgrades[a] (% of overall remaining life)	CRT-P + upgrades[a] (% of overall remaining life)
Implant surgery	0.5	1.8
Postoperative complications	0.1	0.3
Routine upgrades	0.5	0.7
Stable with therapy	95.2	94.4
Lead displacement	0	0.1
Infections	0.1	0.2
HF hospitalisation	3.7	2.4

[a] Numbers are presented to 1 decimal place and so may not sum exactly to 100%.

is useful in many situations, the fact that the ICER is a ratio measure makes the metric unstable. As benefit differences approach zero, the ICER is often difficult to interpret in one-way sensitivity analysis where effects may be non-linear.

Net benefit[131,132] is calculated by first assigning a WTP value to a benefit unit. The incremental benefit of the treatment arm of the model can then be rescaled in terms of cost using this valuation. The net benefit of the treatment can then be calculated by offsetting the incremental cost against the incremental benefits of treatment.

The advantage of reporting net benefit is that it behaves in a more linear way than the ICER and incorporates a notional WTP threshold which makes it easier to interpret. The disadvantage of using net benefit is that it relies on a specific level of valuation for each unit of benefit. In our analysis, we have assumed a WTP threshold of £30,000 per QALY.[133]

Incremental analysis for a shorter time horizon

Some published CRT CEAs, and also the industry submission, use a 5-year rather than no fixed time horizon.[109,111] In order to aid the comparison of the results produced by PenTAG with these other models, the time horizon was fixed to 5 years and the outputs that impact on cost-effectiveness were recorded. These values are shown in *Table 85* in Appendix 7. The shorter time horizon appears to increase the mean ICER for CRT-P from £16,735 per QALY using a lifetime horizon to £24,256 per QALY after 5 years. It should be noted, however, that these analyses with a shortened time horizon will enlist nearly all the costs associated with periodic unit/battery replacement.

Analysis of the age mix of patients enrolled into the CARE-HF study shows that the participants were substantially younger than the age mix used in our model to produce a mixed age cost-effectiveness result (CARE-HF mean age = 65 years, PenTAG mean age = 74 years). The CARE-HF age distribution is shown in *Table 63*.

The model was run using this age mix to explore the effect of uncertainty in the age mix on the cost-effectiveness of CRT-P compared with OPT. The resulting ICER for CRT-P was £15,774, which is 6% lower than for the older age mix.

One-way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied alone, had the greatest impact on the cost-effectiveness of CRT compared with OPT. One-way sensitivity analyses also allow the impact of the uncertainty in each parameter to be assessed.

These analyses examined the impact of:

- **Structural assumptions**. These included changes in time horizon, discount rates for costs and QALYs and device lifetimes.
- **Event probabilities**. These included the probability of experiencing lead displacements, infections, hospitalisations due to HF and arrhythmia.
- **Hazard ratios**. These relate to risks of events with either CRT or ICD devices with which people may have been implanted.
- **Survival curve fitting**. This is the effect of changing the parameters used to define the Weibull curves (and therefore cohort survival).
- **Utility values**. These include separate values for stable with CRT, OPT and ICD. Values for hospitalisation due to HF and each individual NYHA class are also included, in addition to the baseline NYHA patient mix.
- **Costs**. These include the costs of initial implantation, device upgrades, routine device changes and hospitalisations due to sudden or worsening HF problems.

The results of the analyses have been expressed graphically showing the net benefit associated with each new value based on a WTP threshold of £30,000 per QALY. Because of the large numbers of parameters used in the construction of the model, the results have been presented as separate graphs for structural parameters (*Figure 19*), event-related probabilities (*Figure 20*), HRs and survival analysis (*Figure 21*), utilities (*Figure 22*) and costs (*Figure 23*). The base case net benefit has been represented by a vertical line in all figures.

TABLE 63 *Age mix of patients recruited into the CARE-HF trial*

	Age (years)					
	30–39	**40–49**	**50–59**	**60–69**	**70–79**	**80+**
Proportion of participants in category (%)	1.7	6.7	17.8	39.2	28.5	6.1

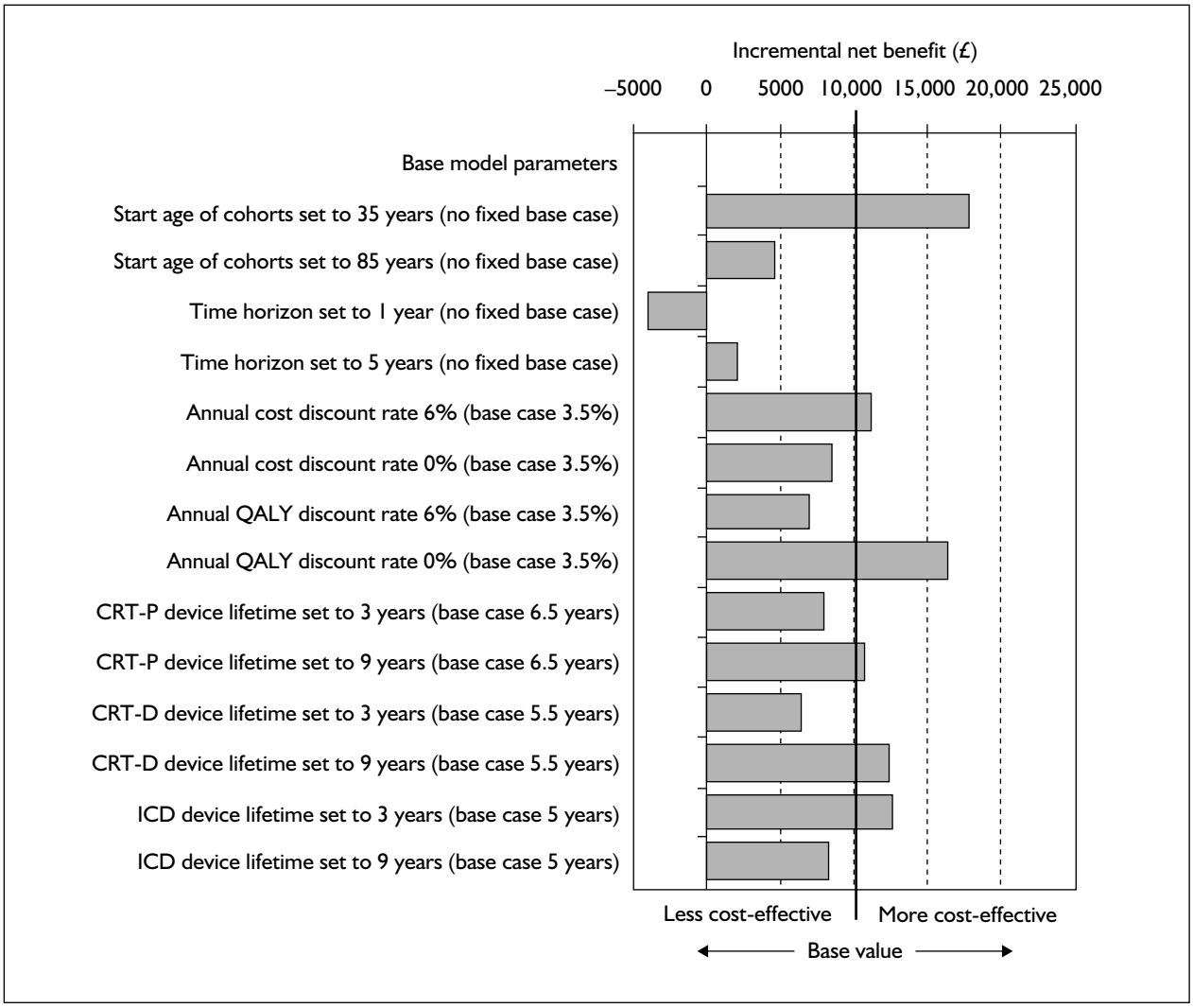

FIGURE 19 *One-way sensitivity analysis for structural inputs: absolute net benefit of CRT-P compared with OPT at a WTP threshold of £30,000/QALY*

Bars to the right of the baseline value represent an increase in incremental net benefit with CRT-P compared with OPT, while those to the left show a reduction in incremental net benefit. The base case ICER is below £30,000 per QALY, so a net benefit reduction of 100% is necessary for an intervention to be cost-ineffective. Such a reduction changes the net benefit from positive to negative.

From this analysis of the effect of changes in individual parameters on the cost-effectiveness of CRT-P compared with OPT, the results appear particularly sensitive to:

1. *Structural parameters*:
   (a) the time horizon of the model
   (b) the age of the person when implanted
   (c) the discount rate applied to health benefits
   (d) the lifetimes of both types of CRT device
2. *Event probabilities*:
   (a) probability of an arrhythmic event with CRT-P
   (b) perioperative death probability
3. *HRs and survival analysis*:
   (a) risk of sudden death with CRT-P
   (b) risk of death as a result of worsening HF with CRT-P
   (c) risk of death as a result of worsening HF with ICD.

Threshold analyses

The one way analyses presented in the previous section reveal the inputs to which the model is most sensitive. A more detailed exploration of these variables was performed to assess where the tipping point occurred. Threshold analysis shows the point at which net benefit changes from being cost-effective to cost-ineffective. The graphical output is again expressed in terms of incremental net benefit

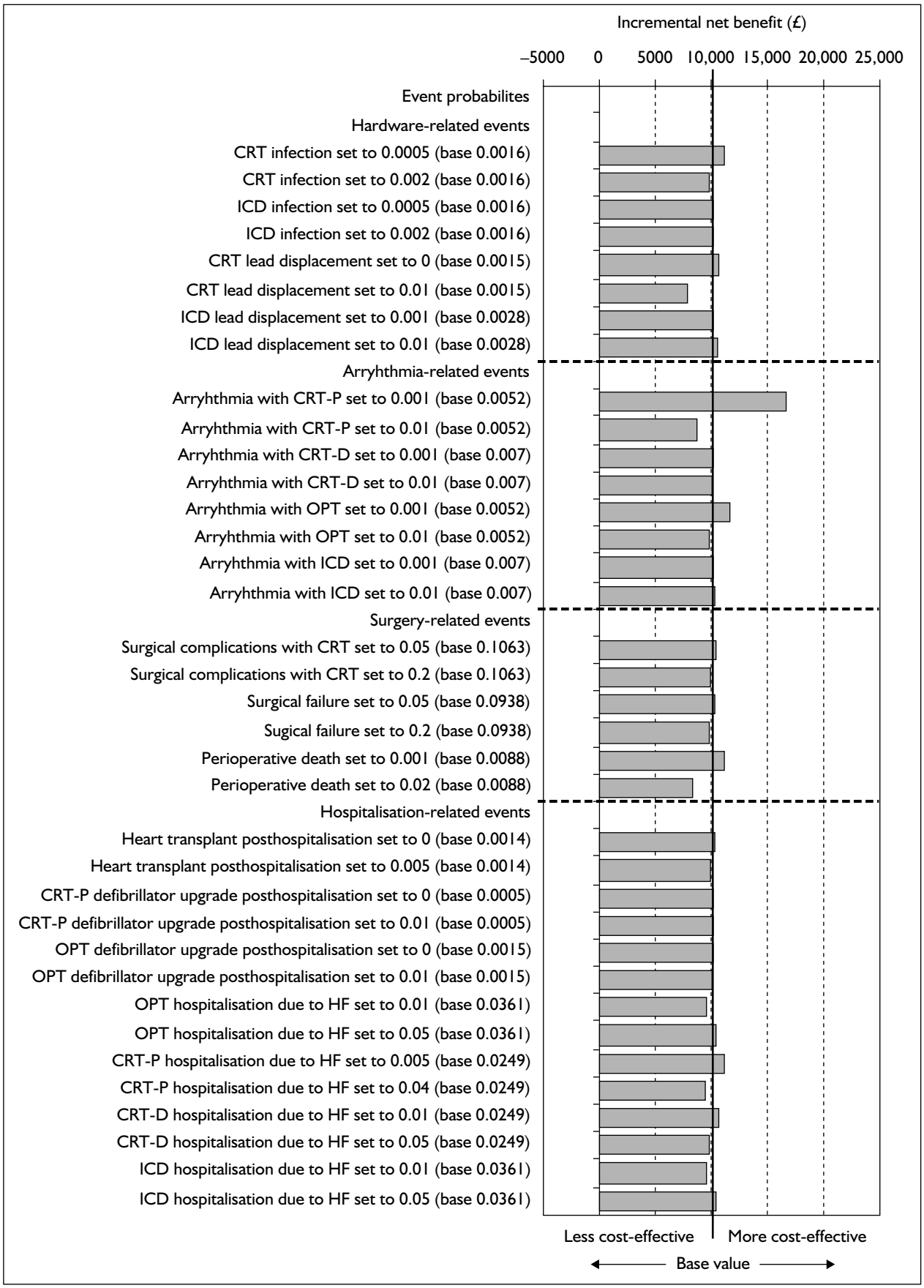

FIGURE 20 *One-way sensitivity analysis for event probabilities: % absolute net benefit of CRT-P compared with OPT at a WTP of £30,000/QALY*

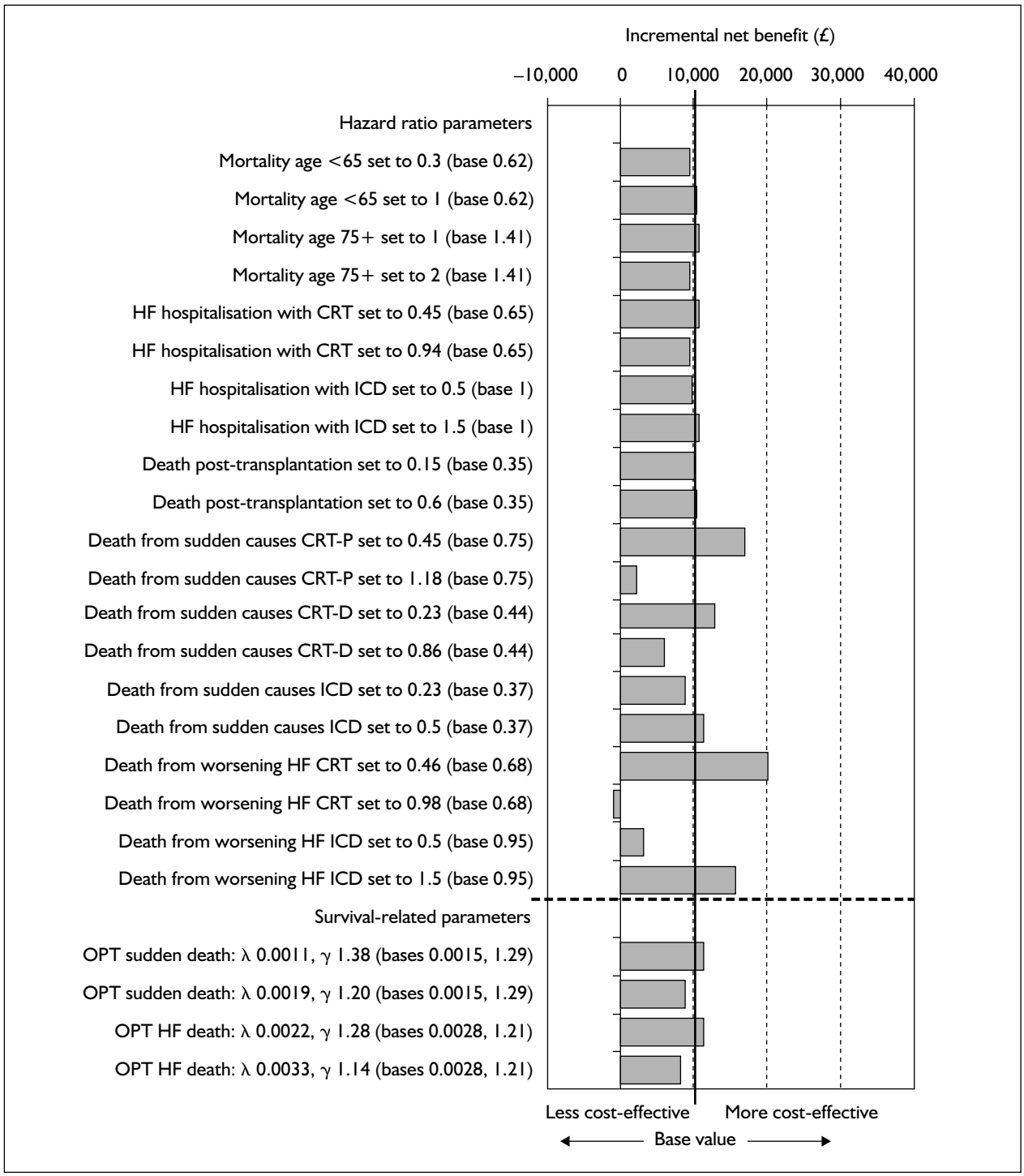

FIGURE 21 *One-way sensitivity analysis for hazard ratio and survival inputs: absolute net benefit of CRT-P compared with OPT at a WTP of £30,000/QALY*

at an assumed WTP threshold of £30,000 per QALY. Cost-effectiveness is again represented as a positive net benefit. CIs were derived from *Table 45*.

Model time horizon

Threshold analysis for the time horizon of the model shows that at a WTP threshold of £30,000 per QALY, treatment with CRT-P versus OPT only becomes cost-effective after approximately 3.75 years (*Figure 24*). At a WTP threshold of £20,000 per QALY, treatment with CRT-P becomes cost-effective after approximately 8 years.

CRT-P device lifetime

Threshold analysis for the expected lifetime of a CRT device shows that at a WTP threshold of

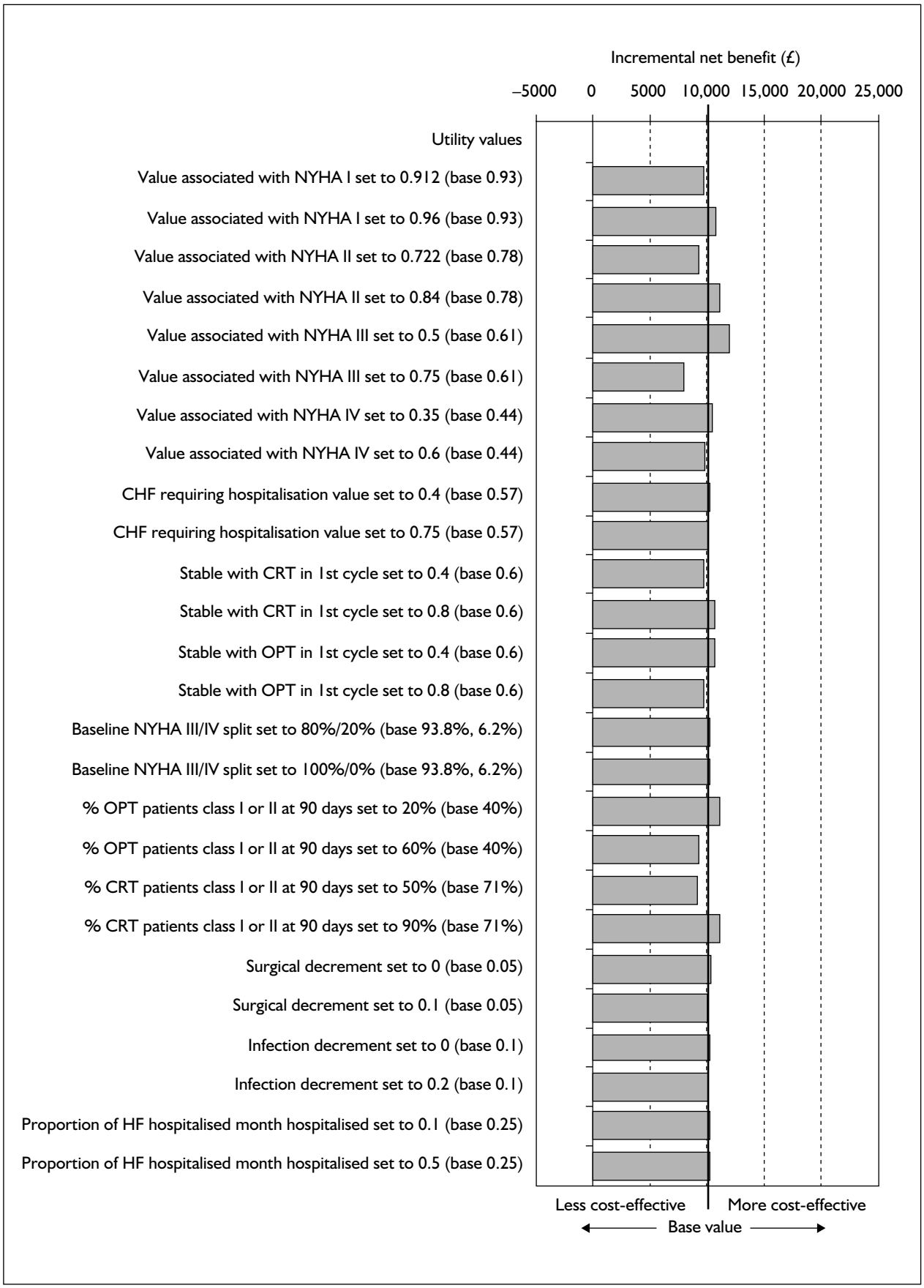

FIGURE 22 *One-way sensitivity analysis for utility inputs in the economic model: absolute net benefit of CRT-P compared with OPT at a WTP of £30,000/QALY. CHF, congestive heart failure.*

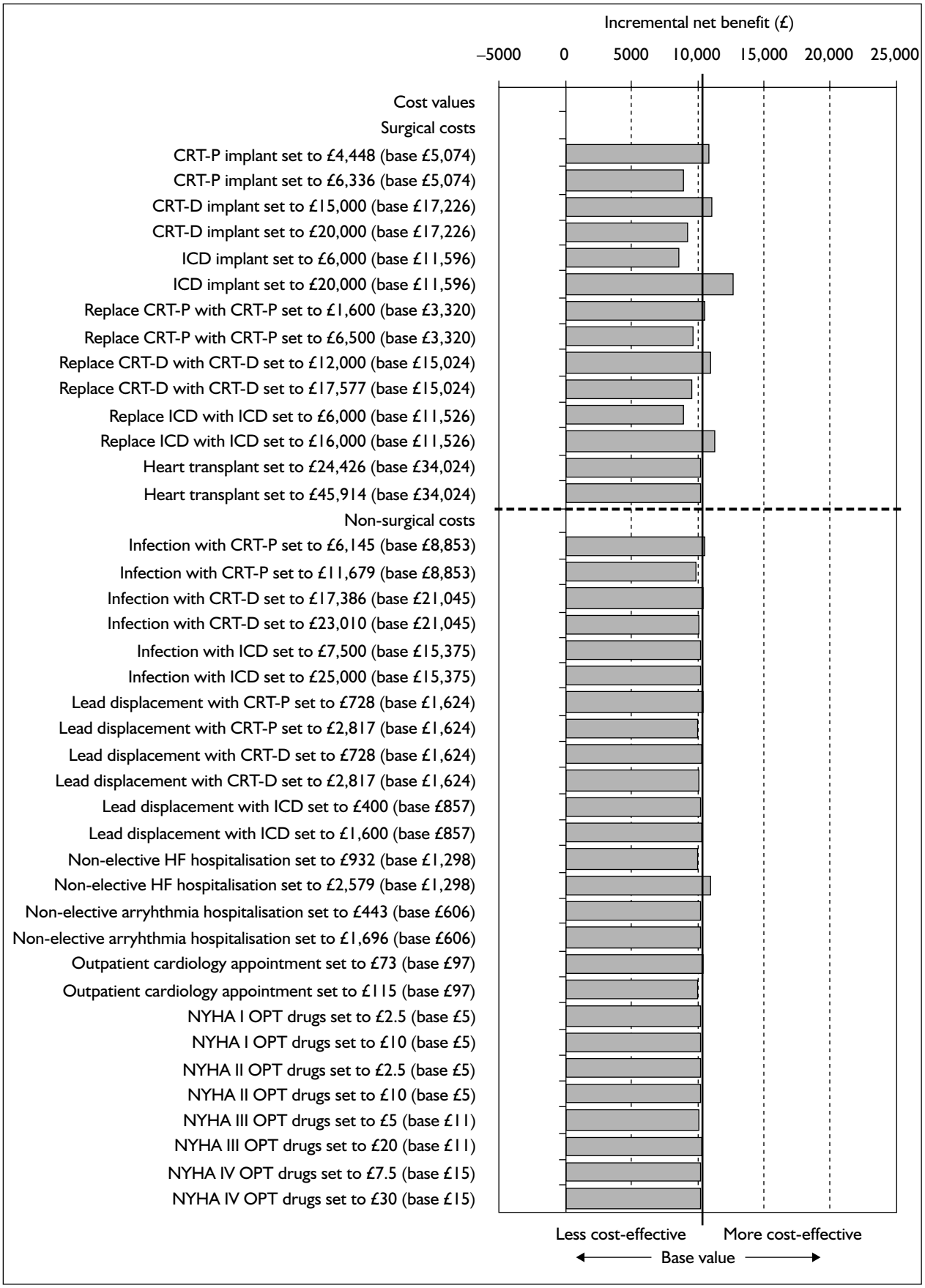

FIGURE 23 *One-way sensitivity analysis for cost inputs in the economic model: absolute net benefit of CRT-P compared with OPT at a WTP of £30,000/QALY*

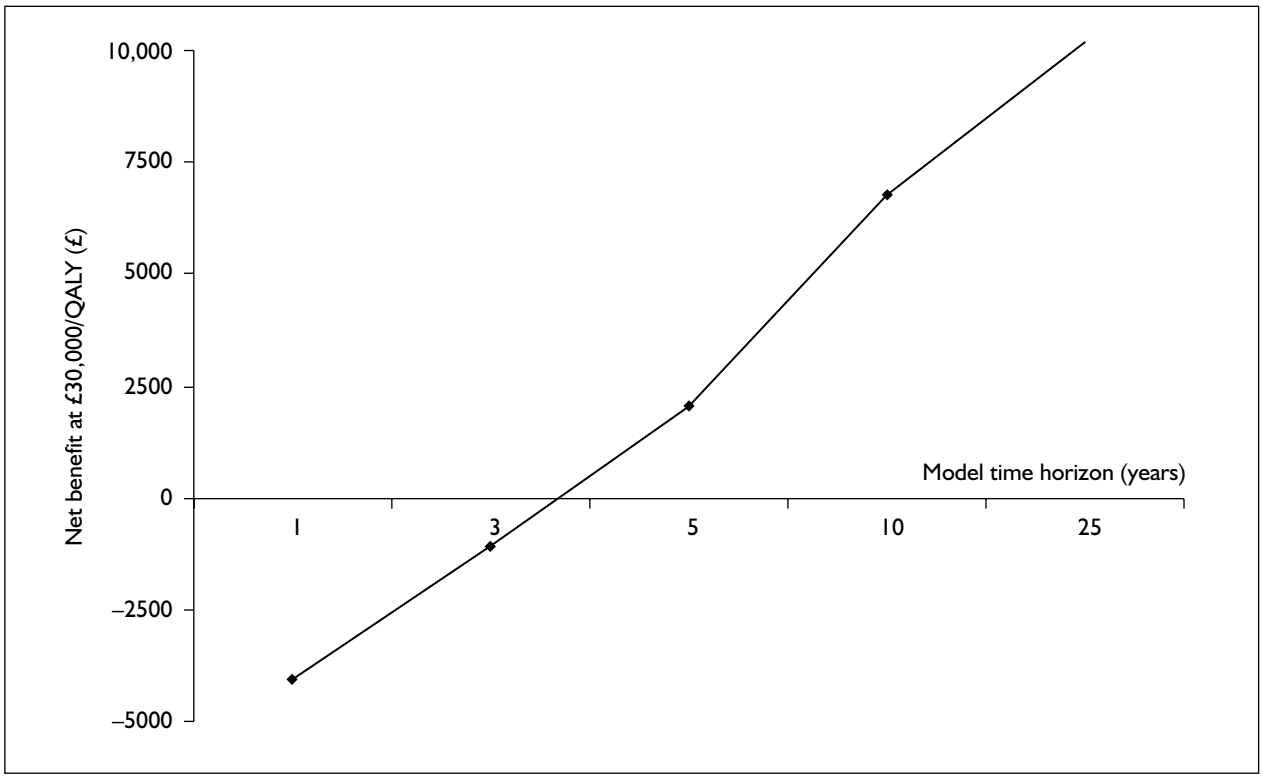

FIGURE 24 *Threshold analysis for model time horizon*

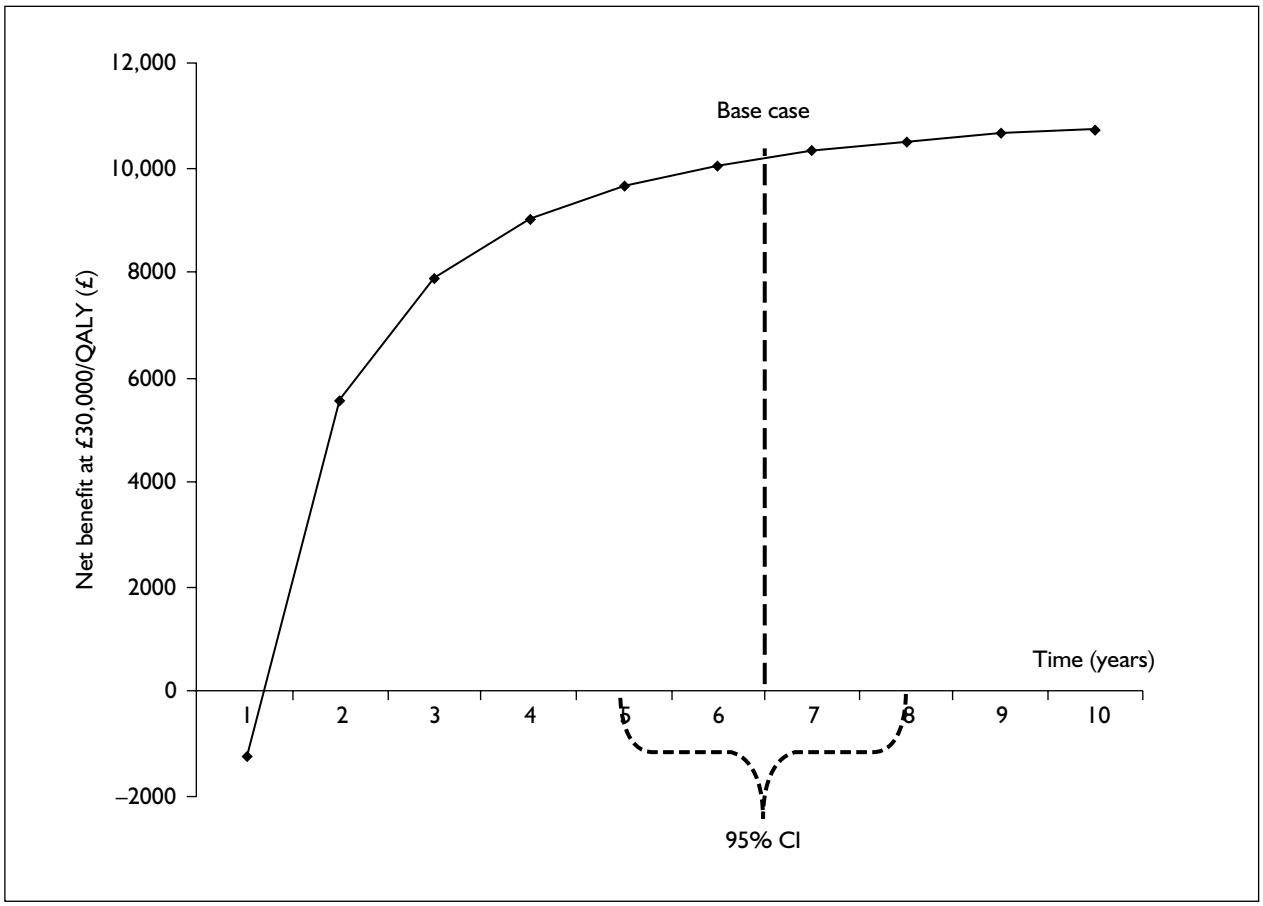

FIGURE 25 *Threshold analysis for CRT-P device lifetime*

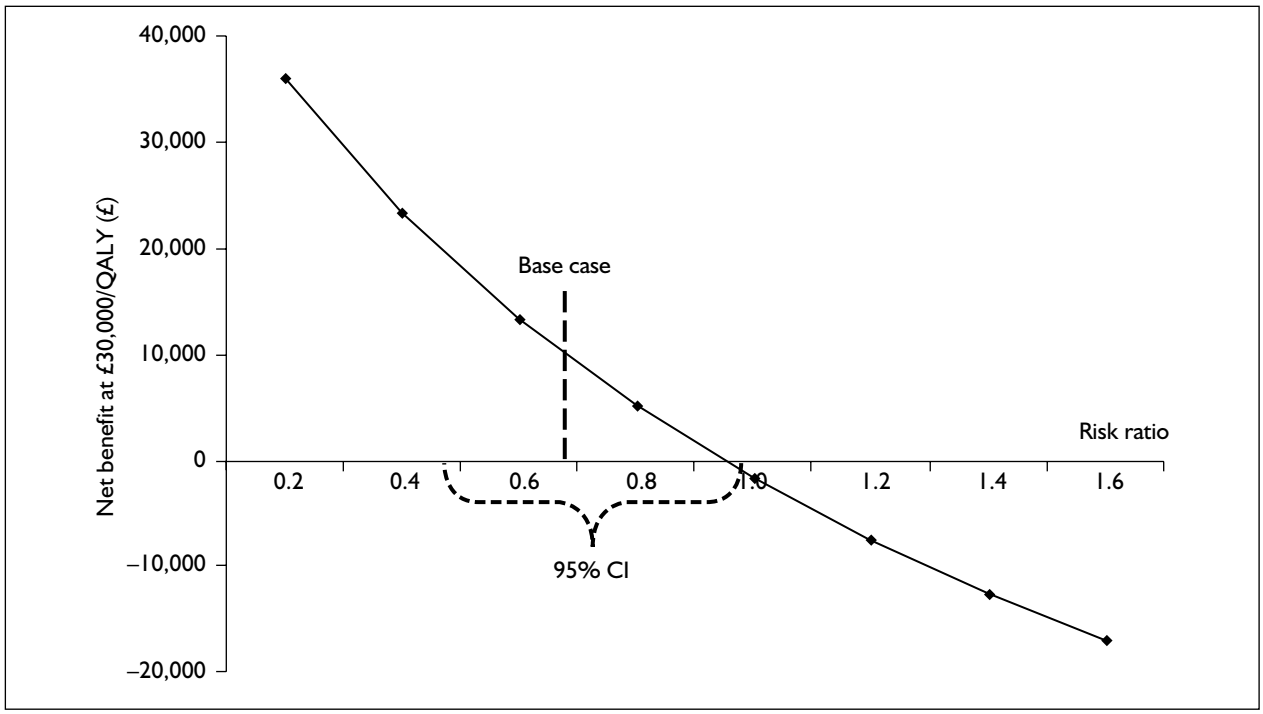

FIGURE 26 *Threshold analysis for risk of death due to worsening HF with CRT device compared with OPT*

£30,000 per QALY, treatment with CRT-P versus OPT only becomes cost-ineffective when the parameter value falls below approximately 1.25 years (*Figure 25*). At a WTP threshold of £20,000 per QALY, CRT-P becomes cost-ineffective when the device lifetime falls below approximately 2.6 years.

Relative risk of death from worsening HF with CRT compared with OPT

Threshold analysis for the risk of death from heart failure when a CRT-P device is compared with OPT shows that at a WTP threshold of £30,000 per QALY the treatment becomes cost-ineffective at an RR value of approximately 0.95 (*Figure 26*). This means that there has to be approximately a 5% reduction in risk of death with the device compared with OPT for the technology to become cost-ineffective. At a WTP threshold of £20,000 per QALY, treatment becomes cost-ineffective at an RR value of approximately 0.8, i.e. when the risk reduction is less than 20%.

Based on the systematic review of trial data, CRT-P implantation currently offers people with HF a 35% reduction in the probability of death compared with OPT only.

Relative risk of sudden cardiac death with CRT-P compared with OPT

Threshold analysis for the risk of death from sudden causes for CRT-P versus OPT shows that at a WTP threshold of £30,000/QALY the treatment becomes cost-ineffective if the risk is approximately 1.3 (*Figure 27*). This means that there has to be an increased risk of death with the device compared with OPT of around 30% for CRT-P to become cost-ineffective. At a WTP threshold of £20,000 per QALY, the treatment becomes cost-ineffective if the risk ratio is above approximately 1, that is, if there is no difference between SCD with the device and with OPT.

Based on the systematic review of trial data, CRT-P implantation currently offers people with HF a 19% reduction in the probability of death compared with OPT only.

Utility associated with patients in NYHA class III

Threshold analysis for the utility associated with patients in NYHA class III in the model shows that at a WTP threshold of £30,000 per QALY there is no feasible parameter value such that CRT-P would be considered cost-ineffective when compared with OPT (*Figure 28*). At a WTP threshold of £20,000 per QALY, treatment with CRT-P becomes cost-ineffective if the utility associated with NYHA class III is greater than approximately 0.9.

Threshold analysis for CRT-P device (pulse generator) cost

The one-way analyses presented in the previous section show the effect on incremental net benefit

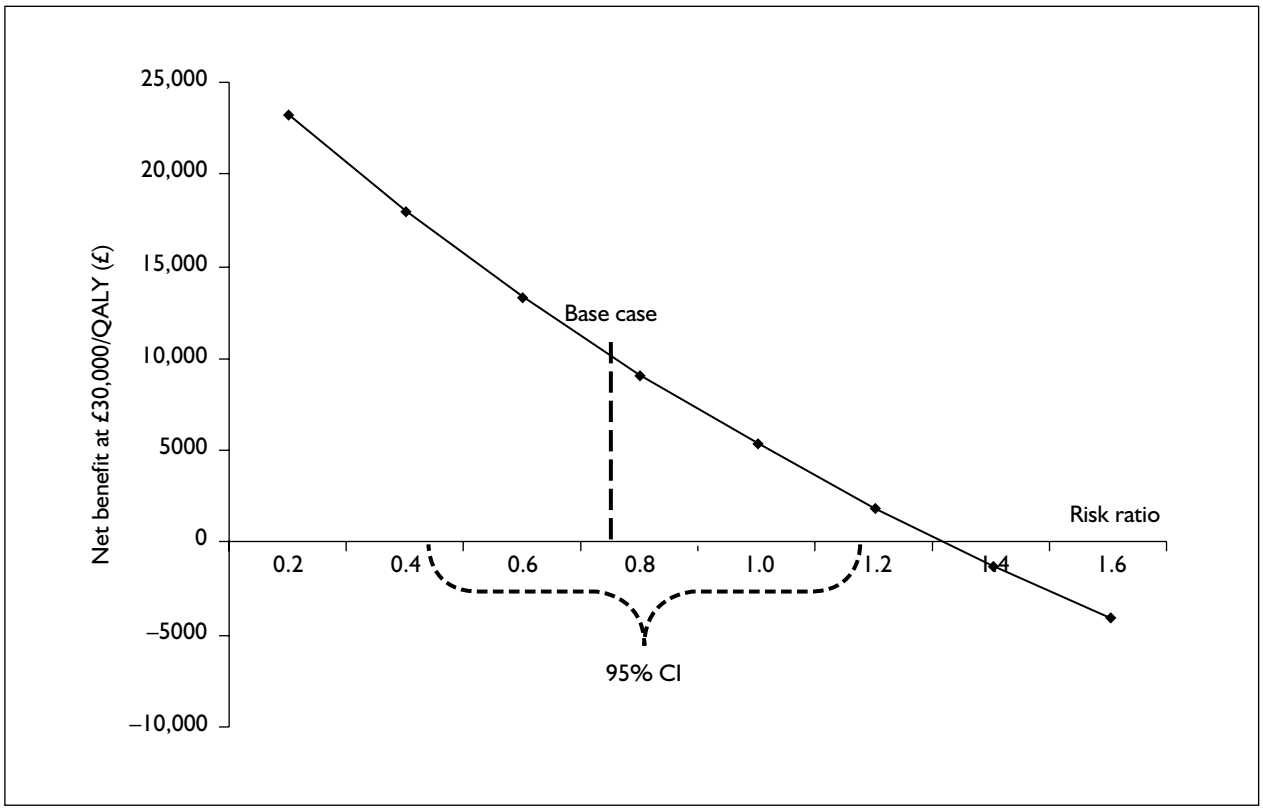

FIGURE 27 *Threshold analysis for risk of sudden death with CRT-P device compared with OPT*

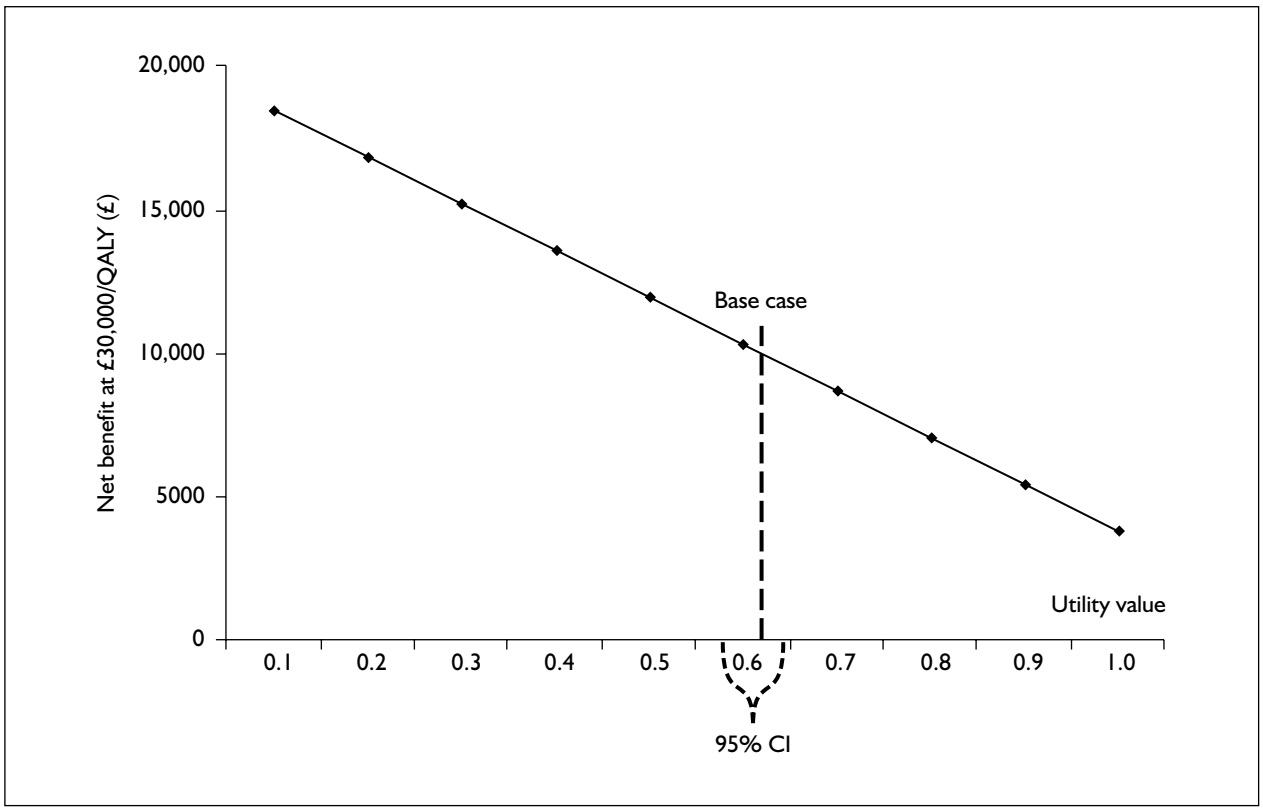

FIGURE 28 *Threshold analysis of NYHA III utility weight*

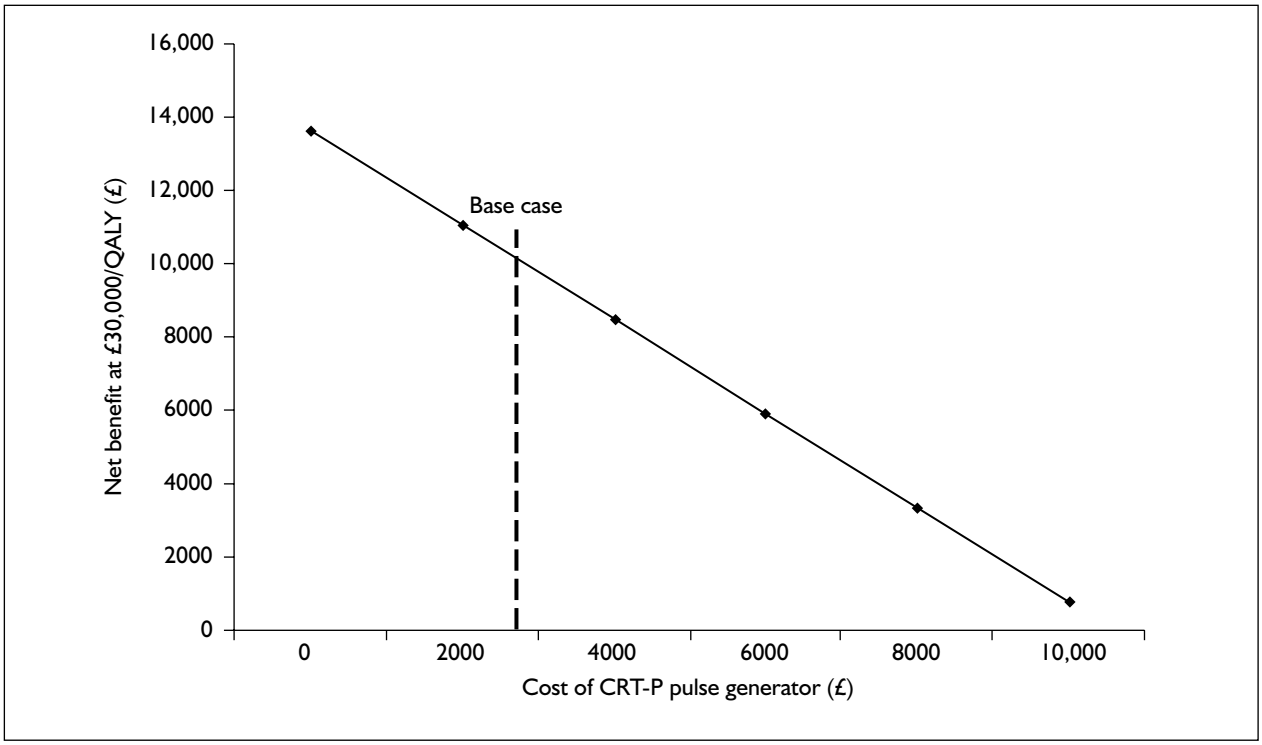

FIGURE 29 *Threshold analysis of CRT-P pulse generator cost*

of individual changes in the costs of initial implantation, routine replacement and the treatment of a device-related infection. However, all involve the cost of a CRT-P pulse generator. A more complete analysis is therefore necessary in order to assess the impact of generator price on cost-effectiveness. *Figure 29* shows the threshold analysis for unit cost of a CRT-P pulse generator when compared with OPT. It shows that at a WTP threshold of £30,000 per QALY, treatment with CRT-P would be considered cost-ineffective if the device cost were increased to more than £10,000 from the current cost of £2687 (as presented in *Table 46*).

At a WTP threshold of £20,000 per QALY, treatment with a CRT-P device becomes cost-ineffective when the generator price rises above approximately £5000.

Probabilistic sensitivity analysis

A Monte Carlo simulation was used to explore the impact of underlying parameter uncertainty on cost-effectiveness. In these simulations, ranges and distributions used were sampled from the events, utility values and costs shown in Appendix 7.

The simulation output (based on 1000 runs of the model) shows that at £20,000 per QALY CRT-P is cost-effective in 68.3% of simulations and at £30,000 per QALY in 91.3% of simulations. CRT-P was dominated in 0.4% of simulations (creating higher costs compared with OPT but lower QALYs). The probabilistic mean ICER is £19,722 (95% CrI £16,235 to £23,210) and the probabilistic median ICER value is £16,805. These values show that the distribution ICERs are highly skewed (skewness coefficient 14.95). This skewness is almost certainly caused by the three points close to the *y*-axis in *Figure 30*.

Outputs from the Monte Carlo simulation are shown graphically in *Figure 30* and the cost-effectiveness acceptability curves (CEACs) for CRT-P are shown in *Figure 31*. The CEACs show that CRT-P would only be considered cost-effective if the WTP threshold was increased beyond approximately £17,000 per QALY.

Value of information analysis

Total expected value of perfect information

An important reason for characterising parameter uncertainty is to establish the value of additional information on any decision made. Expected value of perfect information (EVPI) analysis is derived from the Bayesian approach to modelling.[134] It shows what the maximum gain might be if perfect information were available for the model parameters (that is, if uncertainty were reduced to zero). By using the probabilistic simulation outputs, it is possible to calculate the total value of information estimate for differing levels of WTP.[135]

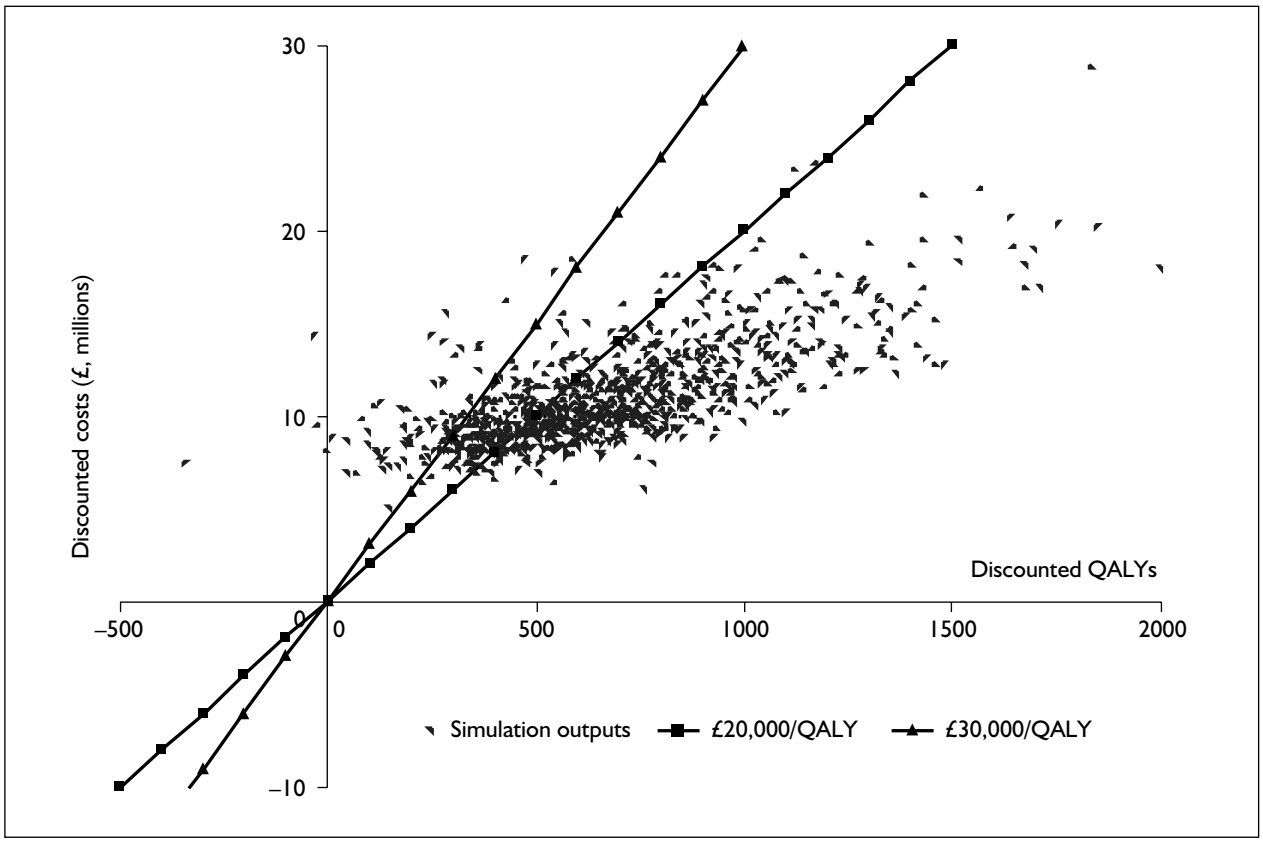

FIGURE 30 *Simulation output (cohort based, 1000 trials) for the cost-effectiveness of CRT-P in comparison with OPT*

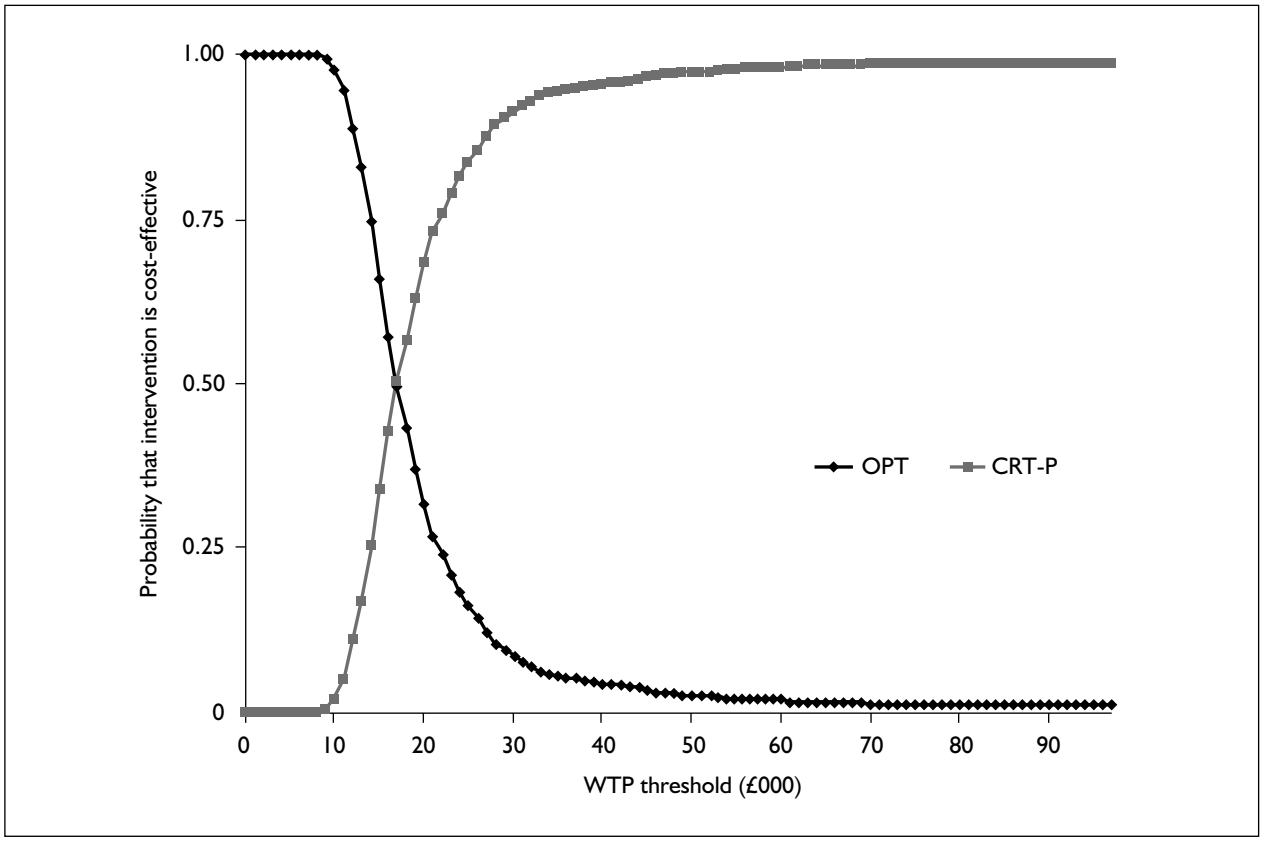

FIGURE 31 *Cost-effectiveness acceptability curves for CRT-P versus OPT*

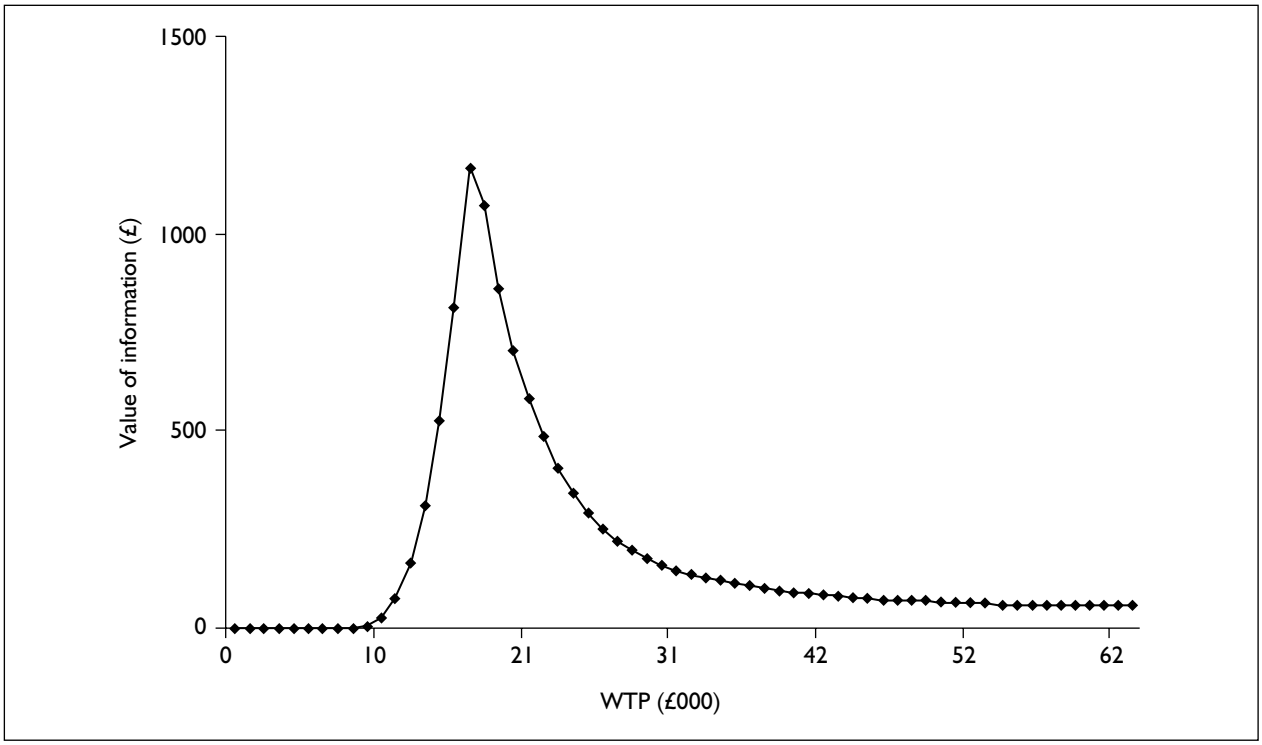

FIGURE 32 *Total EVPI at the patient level (CRT-P versus OPT)*

These are shown in *Figure 32* at the patient level and *Figure 33* at the population level.

Patient-level EVPI for CRT-P versus OPT

At a WTP threshold of £30,000 per QALY, the model predicts that the upper limit of value that could be obtained from acquiring perfect information on all input parameters would be around £157 per person based on the levels of uncertainty recorded for the initial model parameters.

Population-level EVPI for CRT-P versus OPT

To calculate the overall value of perfect information for the total population of people likely to be affected by a decision to implement the use of CRT-P devices, it is necessary to multiply the patient-level value by the total number of people who would be affected over the estimated lifetime of the technology. Based on an assumed 6300 patients per year in England and Wales receiving CRT[7] and a decision horizon of 7 years (approximately the mean lifetime of a CRT-P device), the total EVPI at the population level is £6.2 million. The calculation was performed using a WTP threshold of £30,000 per QALY.

The population EVPI figure represents the upper boundary of the value of future research on the decision problem. The value of information in this case is £6.2 million and suggests that further research could reduce decision uncertainty.

Total expected value of perfect parameter information

The results of the PSA relating to the likelihood of CRT-P being cost-effective compared with OPT showed that decision uncertainty is low. This means that further information is unlikely to make a great difference to decision-making and so the EVPI is relatively small. However, a more comprehensive analysis is necessary to evaluate the impact of reducing all uncertainty in individual parameters or groups of parameters on decision uncertainty; this is the expected value of perfect parameter information (EVPPI) analysis.

However, EVPPI results depend critically on the variance recorded for each input parameter and on a fixed WTP threshold. EVPPI outputs should therefore be interpreted with some caution.

It is also important to note that the sum of the EVPPI values may be more than or less than the value of perfect information for all parameters.[136]

Performing a full EVPPI analysis is extremely computationally intensive. The complexity of the PenTAG model meant that a complete investigation of EVPPI for every model parameter was not possible. Instead, a pragmatic iterative

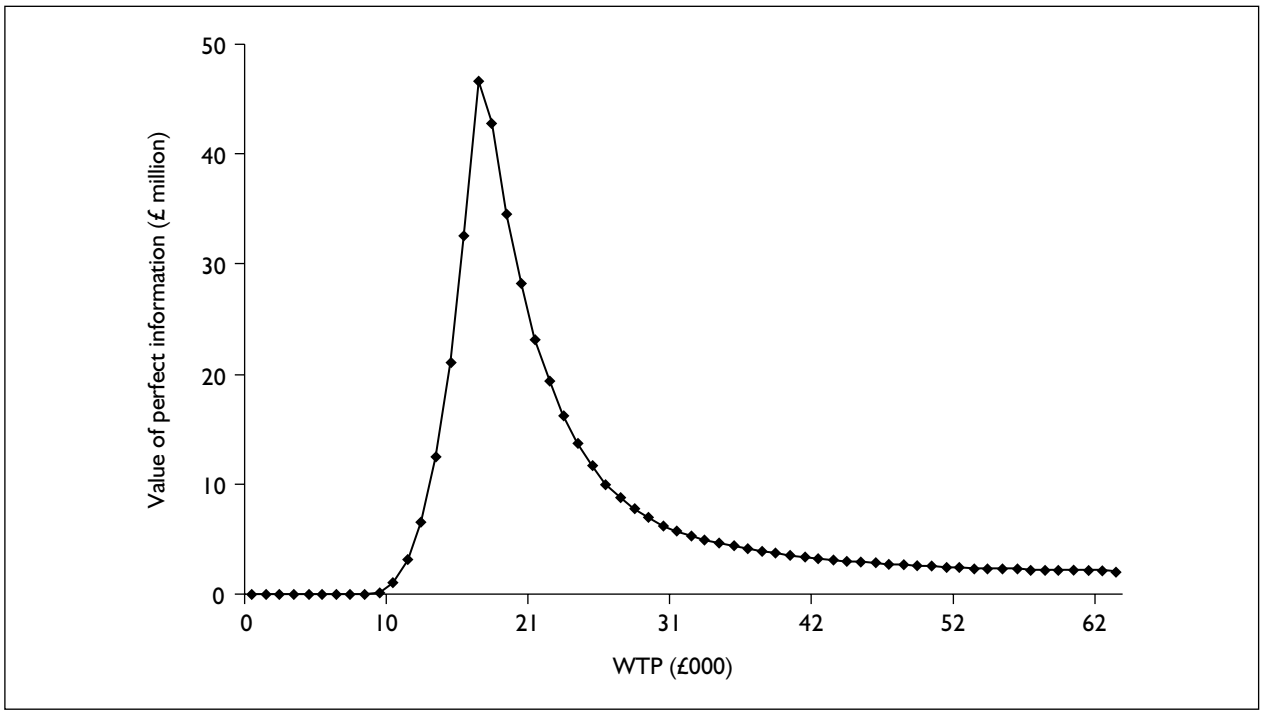

FIGURE 33 *Total EVPI at the population level (CRT-P versus OPT)*

approach was taken. Initially the analysis was performed for groups of parameters (transition probabilities, HRs, parameters used to define survival curves in people on OPT, costs and utilities). The key groups identified by this first stage were then broken down to produce values for individual parameters within the group. EVPPI results from both stages of the analysis for CRT-P Vs OPT are shown in *Figure 34*.

The results show that the maximum reduction in decision uncertainty is £2,354.829 for all HRs and £1,144,427 for all survival curves. Therefore, further information on these parameters could

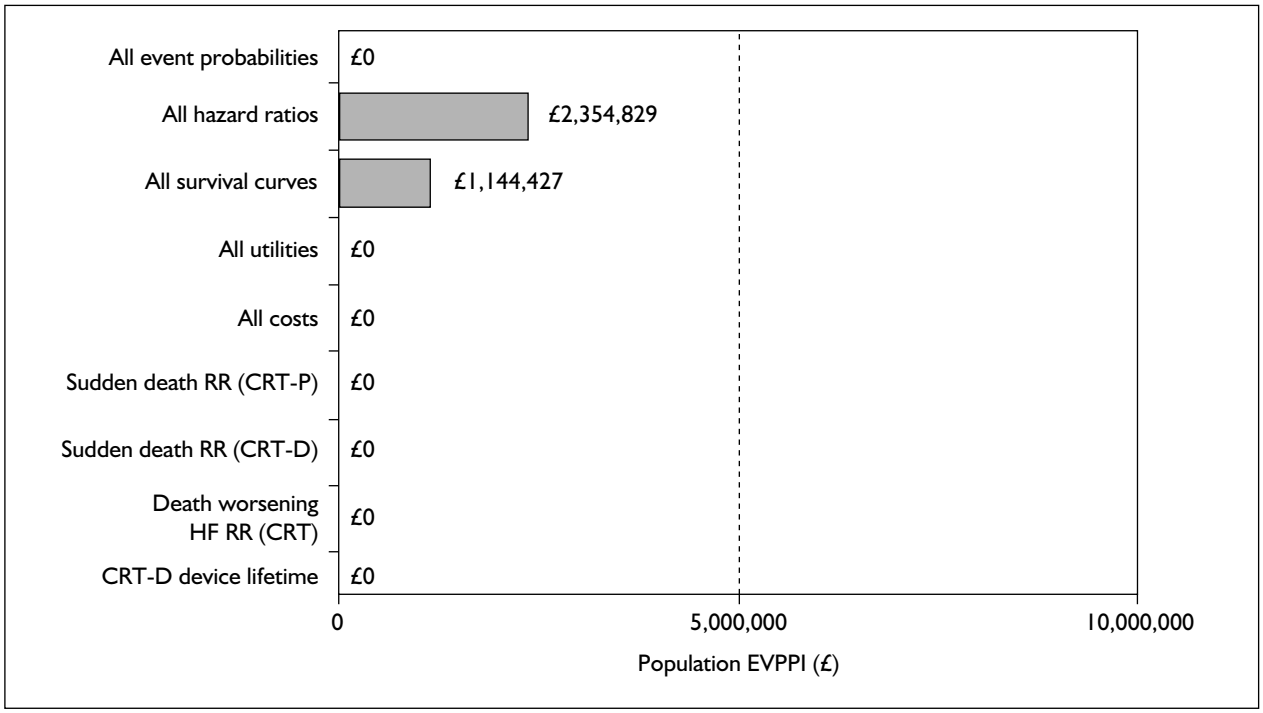

FIGURE 34 *EVPPI at the population level (CRT-P versus OPT)*

TABLE 64 *Discounted base case cost-effectiveness results per person for CRT-D compared with OPT (lifetime time horizon), by age and mixed age cohort*

Start age (years)	OPT costs (£)	OPT QALYs	CRT-D costs (£)	CRT-D QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
30	17,673	5.52	48,568	7.21	30,895	1.69	18,289
40	17,422	5.45	47,907	7.09	30,485	1.63	18,666
50	16,601	5.22	45,976	6.71	29,375	1.49	19,677
60	13,863	4.44	40,808	5.71	26,945	1.26	21,356
70	10,030	3.31	34,129	4.40	24,099	1.08	22,231
80	7,422	2.52	29,125	3.39	21,703	0.86	25,110
90	5,933	2.07	26,015	2.71	20,082	0.64	31,186
Mixed	**9,367**	**3.10**	**32,687**	**4.09**	**23,320**	**0.99**	**23,650**

have a significant impact on decision uncertainty. Further information on other parameters would have a negligible impact.

Cost-effectiveness of CRT-D compared to OPT

Note: This pairwise comparison was specified in the NICE appraisal scope and assessment protocol, and the full results are therefore presented in this section for completeness. However, the usefulness to decision-makers of making this cost-effectiveness comparison is highly questionable, because the obvious comparator for CRT-D should be the next cheapest and effective alternative health technology for this patient group, that is, CRT-P, not OPT.

Base case results for cost-effectiveness

Base case results produced by the economic model for different cohort starting ages and for the overall mixed age cohort are shown in *Table 64* on a per-person basis. For the mixed age cohort, in comparison with OPT the implantation of a CRT-D device provides an extra 0.99 QALYs (360 quality-adjusted days); however, this improvement would cost the NHS £23,320 per person to achieve.

In general, the ICER increases non-linearly with age, with only the oldest patients being above the assumed WTP for a QALY.

Model outputs and model validation

Event counts

The aggregated event counts produced in the CRT-D and OPT arms of the model are shown in *Table 65*.

The model predicts a 16% reduction in the number of hospitalisations due to worsening HF over the average person's remaining life in people with a CRT-D device implanted compared with people receiving OPT.

Survival

Table 66 summarises model outputs relevant to patient survival in patients with a CRT-D device. *Table 67* shows age-dependent survival gains for CRT-D compared with OPT. As was the case in the assessment of CRT-P against OPT, both expected median and mean survival have been included.

Table 67 shows that people with a CRT-D device can expect to live, on average, approximately 1.3 years longer than people on OPT.

The overall trial-based pooled risk reduction for all-cause mortality for CRT-D versus OPT was 0.65 (95% CI 0.49 to 0.85). The model produces a similar result (risk reduction 0.750, 95% CrI 0.745 to 0.756).

State occupancy

The state occupancies for both the CRT-D and OPT arms of the model are presented in *Table 68*. Meta-states have been created for the purposes of presentation. All forms of death have again been excluded.

People in both arms of the model spend most of their expected average remaining life in the 'stable' meta-state. The only other meta-state where people spend any significant amount of time alive is 'HF hospitalisation'. As is to be expected, people on OPT spend more time in that meta-state than people with a CRT device due to the benefits provided by the pacemaker.

Incremental analysis for a shorter time horizon

As for the CRT-P cost-effectiveness, a comparison of the results produced by PenTAG with other models, with the time horizon fixed to 5 years, was undertaken (see Appendix 7).

TABLE 65 *Patient-relevant outcomes in the model for each mixed age cohort of 1000 people*

	OPT + upgrades (%)		CRT-D + upgrades (%)		Difference (%)
	Event likelihood over time	Event rate per 100 patient-years	Event likelihood over time	Event rate per 100 patient-years	
Lead infection	4.5	0.93	17.1	3.00	+12.6
Lead displacement	0	NA	11.6	1.98	+11.6
Total routine device changes	28.7	NA	68.2	NA	+39.5
CRT-P	0	NA	0.0	NA	NA
CRT-D	0	NA	67.5	NA	+67.5
ICD	28.7	NA	0.6	NA	–28.0
Device upgrades	32.0	NA	0.7	NA	–31.3
CRT-D	0	NA	0.0	NA	NA
ICD	32.0	NA	0.6	NA	–31.3
Serious arrhythmic event	32.0	7.82	0.7	0.11	–31.3
Surgical complication	7.4	1.57	20.7	3.71	+13.8
Surgical failure	0		2.7	0.43	+2.7
Heart transplant	0.3	0.1	0.3	0.04	+0.0
Hospitalisation as a result of HF	2.36	47.8	1.98	31.7	–0.38

NA, not applicable.

TABLE 66 *Survival outputs for people in CRT-D arm, by age and mixed age cohort*

Start age (years)	25% centile (years)	Median survival (years)	75% centile (years)	Mean survival (years)
30	5.00	10.23	17.85	12.7
40	5.00	10.15	17.62	12.2
50	4.92	9.85	16.39	11.2
60	4.69	7.85	12.62	9.0
70	3.00	5.77	9.08	6.7
80	1.92	4.23	6.85	5.0
90	1.31	2.92	5.46	3.9
Mixed	**2.31**	**5.08**	**8.46**	**6.2**

TABLE 67 *Additional life for people in the CRT-D arm compared with the OPT arm of the PenTAG model*

Start age (years)	25% centile (years)	Median survival (years)	75% centile (years)	Mean survival (years)	Proportional increase in overall survival (%)
30	1.54	2.92	4.39	3.0	40.0
40	1.62	2.92	4.23	2.7	40.4
50	1.54	2.69	3.31	2.3	37.6
60	1.39	1.69	2.69	1.8	27.5
70	0.92	1.31	1.92	1.4	29.3
80	0.54	1.15	1.39	1.1	37.5
90	0.31	0.62	1.15	0.8	26.6
Mixed	**0.62**	**1.31**	**1.77**	**1.3**	**34.7**

TABLE 68 *Overall state occupancies per person in the economic model for mixed age cohorts of 1000 people (excluding all death states)*

	OPT + upgrades (% of overall remaining life)	CRT-D + upgrades (% of overall remaining life)
Implant surgery	0.5	1.2
Postoperative complications	0.1	0.3
Routine upgrades	0.5	0.8
Stable with therapy	95.2	94.9
Lead displacement	0.0	0.1
Infections	0.1	0.2
HF hospitalisation	3.7	2.4

Sensitivity analysis

One-way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied independently of all other model inputs, had the greatest impact on the incremental cost-effectiveness of CRT-D compared with OPT.

The results of the analyses have been expressed graphically, showing the absolute net benefit associated with each new value based on a WTP threshold of £30,000 per QALY. Because of the large numbers of parameters used in the construction of the model, the results have been presented as separate graphs for structural parameters (*Figure 35*), event-related probabilities (*Figure 36*), HRs and survival analysis (*Figure 37*), utilities (*Figure 38*) and costs (*Figure 39*). Baseline net benefit is again shown by a vertical line.

Bars to the right of the baseline value represent an increase in incremental net benefit with CRT-D compared with OPT, whereas those to the left show a reduction in incremental net benefit. The baseline ICER is below £30,000 per QALY and so a net benefit reduction of 100% is necessary for an intervention to be cost-ineffective. Such a reduction changes the net benefit from positive to negative.

In the (deterministic) analysis of the effect of changes in input parameters on the cost-effectiveness of CRT-D compared with OPT, the model appears particularly sensitive to:

1. *Structural parameters*:
   (a) model time horizon
   (b) discount rate applied to health benefits
   (c) CRT-D device lifetime
2. *Event probabilities*:
   (a) probability of lead displacement with a CRT-D device
   (b) probability of infection with a CRT-D device
3. *HRs and survival analysis*:
   (a) risk of sudden death with CRT-D
   (b) risk of death as a result of worsening HF with CRT-D.

The model appears relatively stable to changes in cost and utility parameters. The utilities associated with each NYHA class, CRT-D implant and re-implant had an important effect on incremental net benefit. Only costs associated with CRT-D device implant and replacement had any effect on baseline cost-effectiveness.

Threshold analysis

The one-way sensitivity analyses presented in the previous section reveal the inputs to which parameter uncertainty had the greatest effect on the cost-effectiveness of CRT-D compared with OPT. Threshold analyses were performed on parameters that resulted in the largest swings in absolute net benefit.

Model time horizon

Threshold analysis for the time horizon of the model shows that at a WTP threshold of £30,000 per QALY, treatment with CRT-D becomes cost-effective after approximately 8 years (*Figure 40*). The weighted mean time horizon is approximately 26 years. At a WTP threshold of £20,000 per QALY, treatment with CRT-P never becomes cost-effective over the average lifetime that a person spends in the model.

CRT-D device lifetime

At a WTP threshold of £30,000 per QALY, treatment with CRT-D only becomes cost-ineffective when the device lifetime falls below approximately 4 years. As the lifetime of a device increases beyond the current expected value, there is a slight increase in the incremental net benefit of CRT-D compared with OPT (*Figure 41*). At a

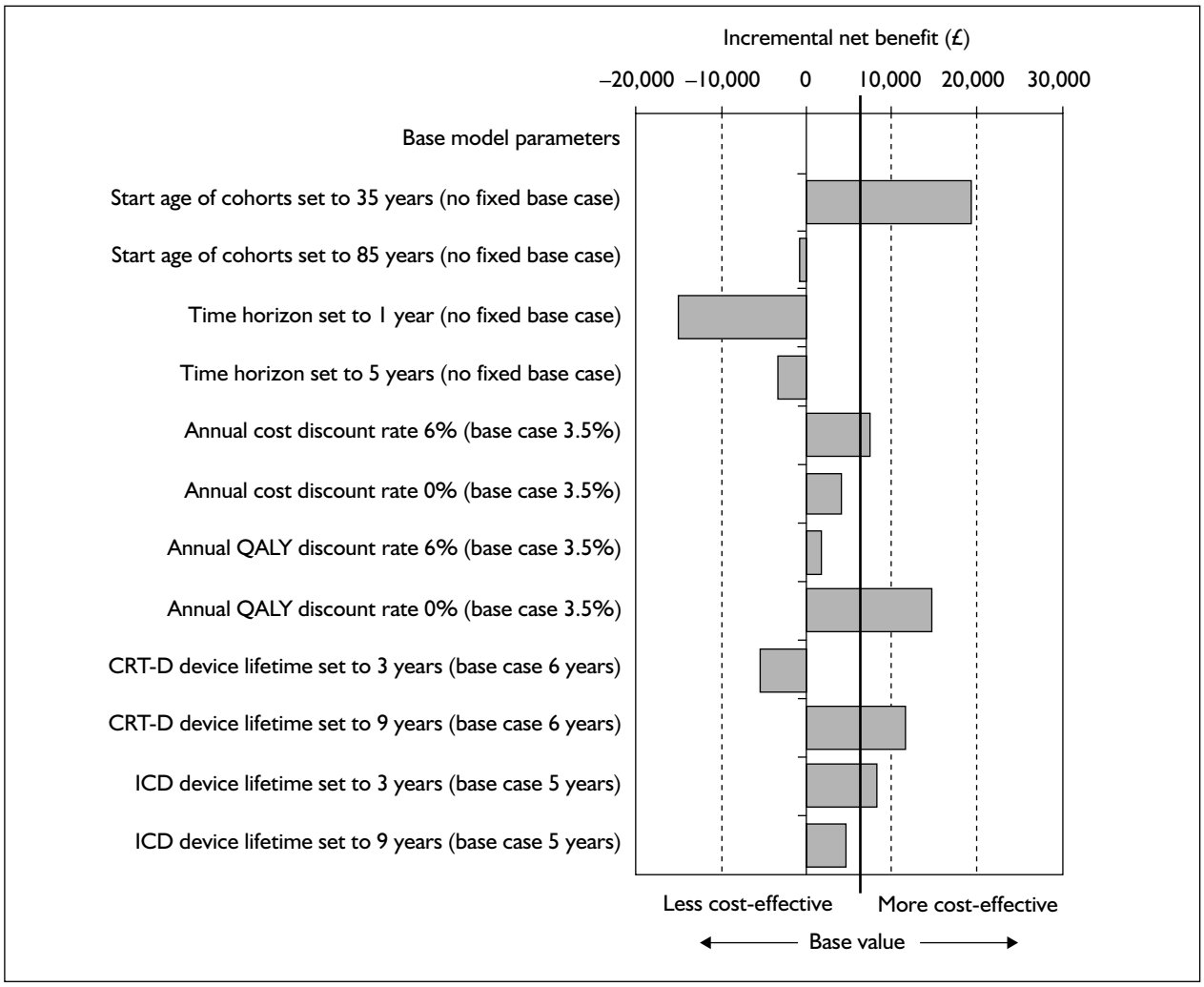

FIGURE 35 *One-way sensitivity analysis for structural inputs in the economic model: absolute net benefit of CRT-D compared with OPT at a WTP of £30,000/QALY*

WTP threshold of £20,000 per QALY, treatment with CRT-D becomes cost-effective if the average lifetime of a device increases to approximately 7.5 years.

Relative risk of death from worsening HF with CRT-D compared with OPT

Figure 42 shows the threshold analysis for the risk of death from HF in patients with a CRT-D device compared with those on OPT. At a WTP threshold of £30,000 per QALY, treatment with CRT-D becomes cost-effective if the parameter value is greater than approximately 0.8. The baseline parameter used in the model is 0.68 (95% CI 0.46 to 0.98). *Figure 42* shows that small changes in the parameter value result in large changes in net benefit.

At a WTP threshold of £20,000 per QALY, treatment with CRT-D becomes cost-effective if the parameter value is below approximately 0.55. Therefore, there would have to be at least a 45% reduction in the risk of death with a CRT-D compared with OPT for it to be considered cost-effective.

Risk of sudden cardiac death with CRT-D device compared with OPT

Figure 43 shows the threshold analysis for the risk of SCD in patients with a CRT-D device compared with those on OPT. There is a nearly linear relationship between the interventions incremental net benefit and model parameter. At a WTP threshold of £30,000 per QALY, treatment with CRT-D becomes cost-ineffective when the parameter value is greater than approximately 0.65. The baseline value used in the model is 0.44 (95% CI 0.23 to 0.86).

At a WTP threshold of £20,000 per QALY, treatment with CRT-D becomes cost-effective if the parameter value is below approximately 0.25. This

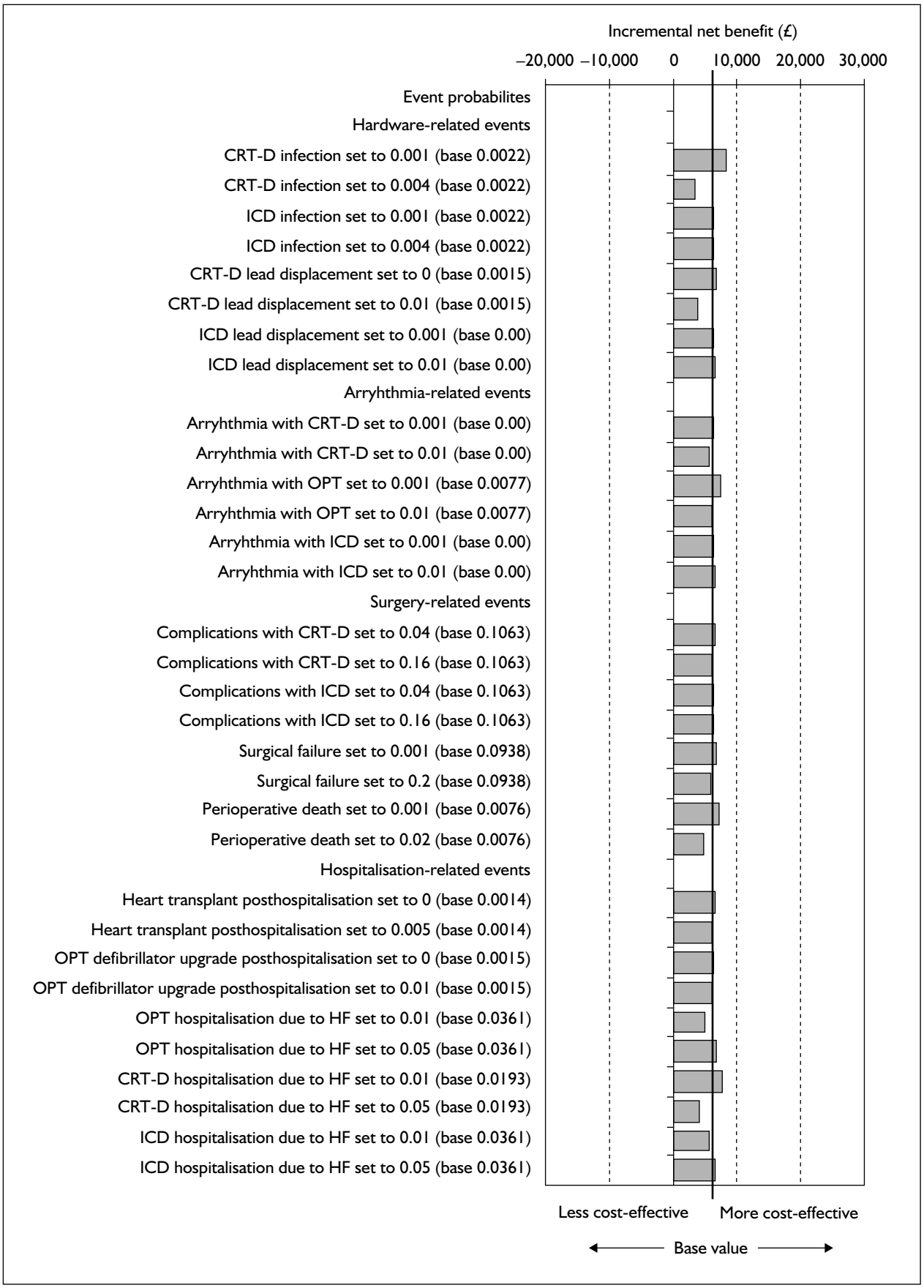

FIGURE 36 *One-way sensitivity analysis for event probabilities in the economic model: absolute net benefit of CRT-D compared with OPT at a WTP of £30,000/QALY*

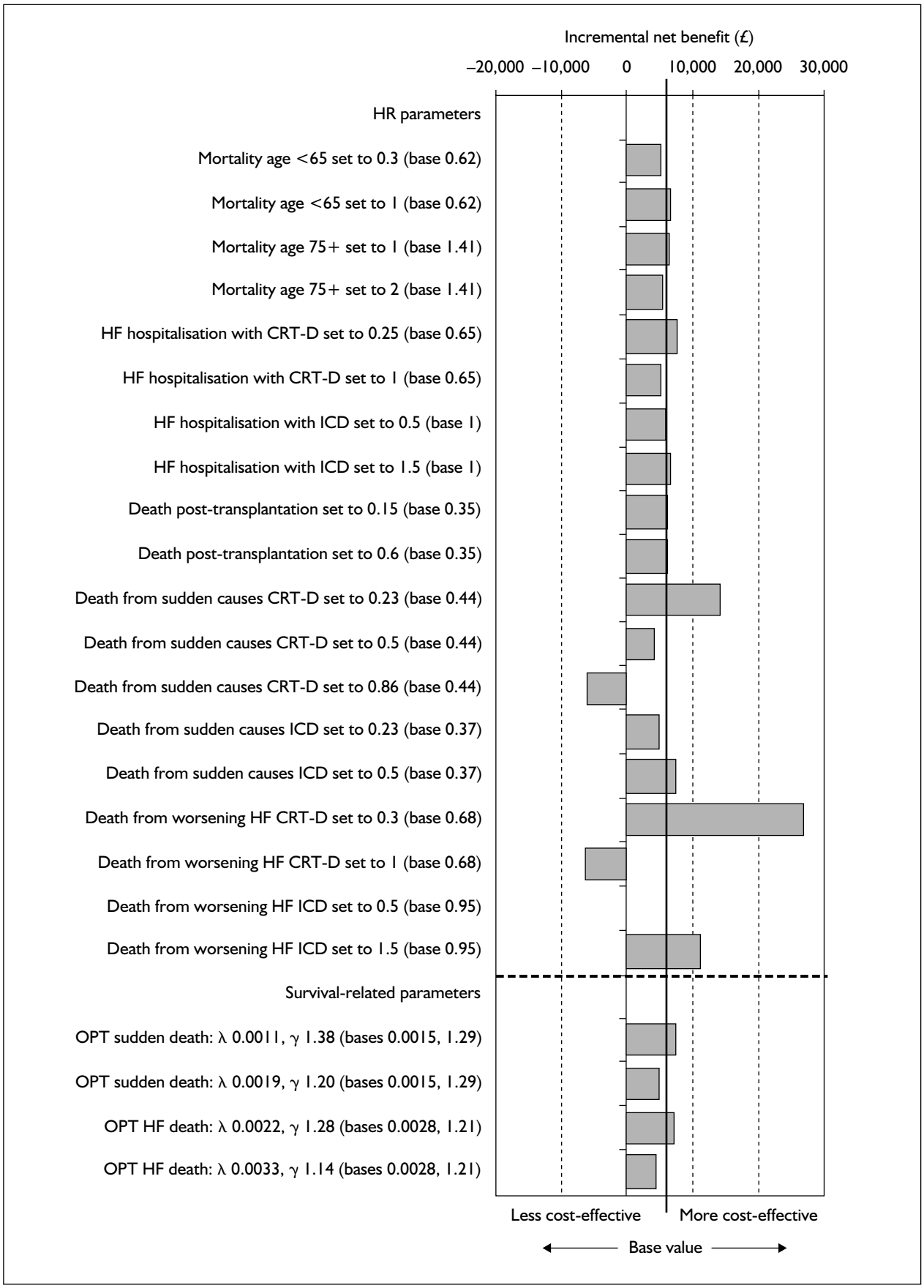

FIGURE 37 *One-way sensitivity analysis for HR and survival inputs in the economic model: absolute net benefit of CRT-D compared with OPT at a WTP of £30,000/QALY*

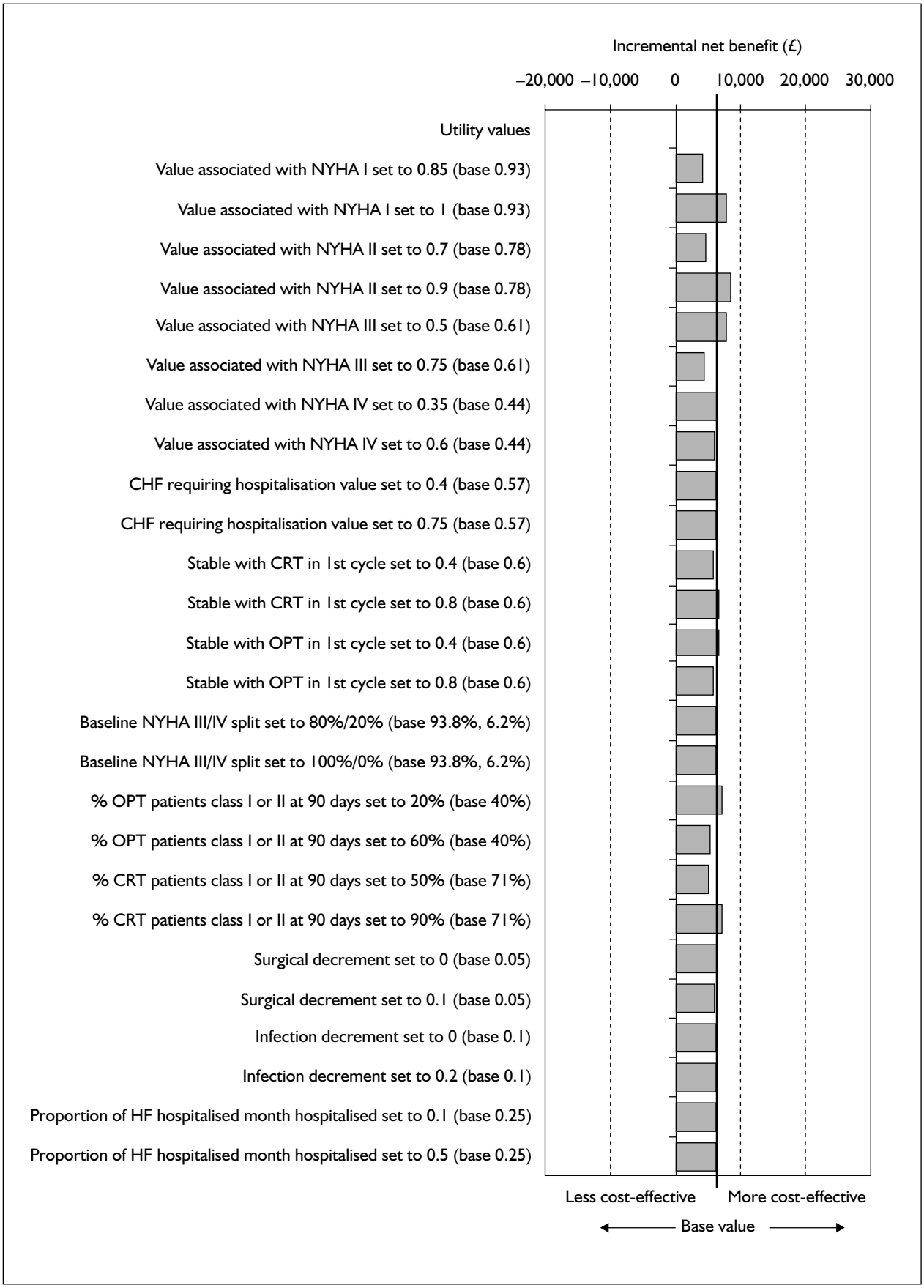

FIGURE 38 *One-way sensitivity analysis for utility inputs in the economic model: absolute net benefit of CRT-D compared with OPT at a WTP of £30,000/QALY*

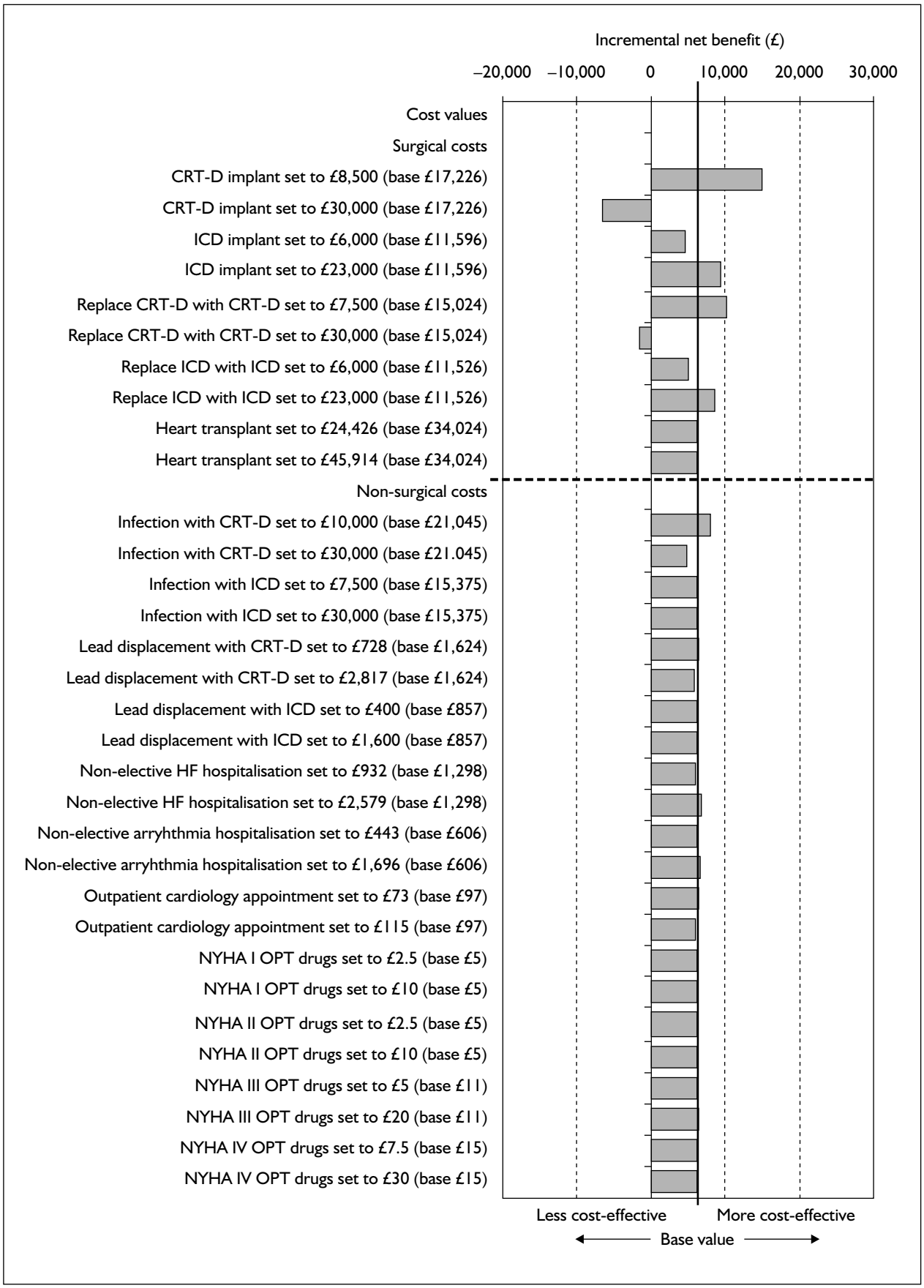

FIGURE 39 *One-way sensitivity analysis for cost inputs in the economic model: absolute net benefit of CRT-D compared with OPT at a WTP of £30,000/QALY*

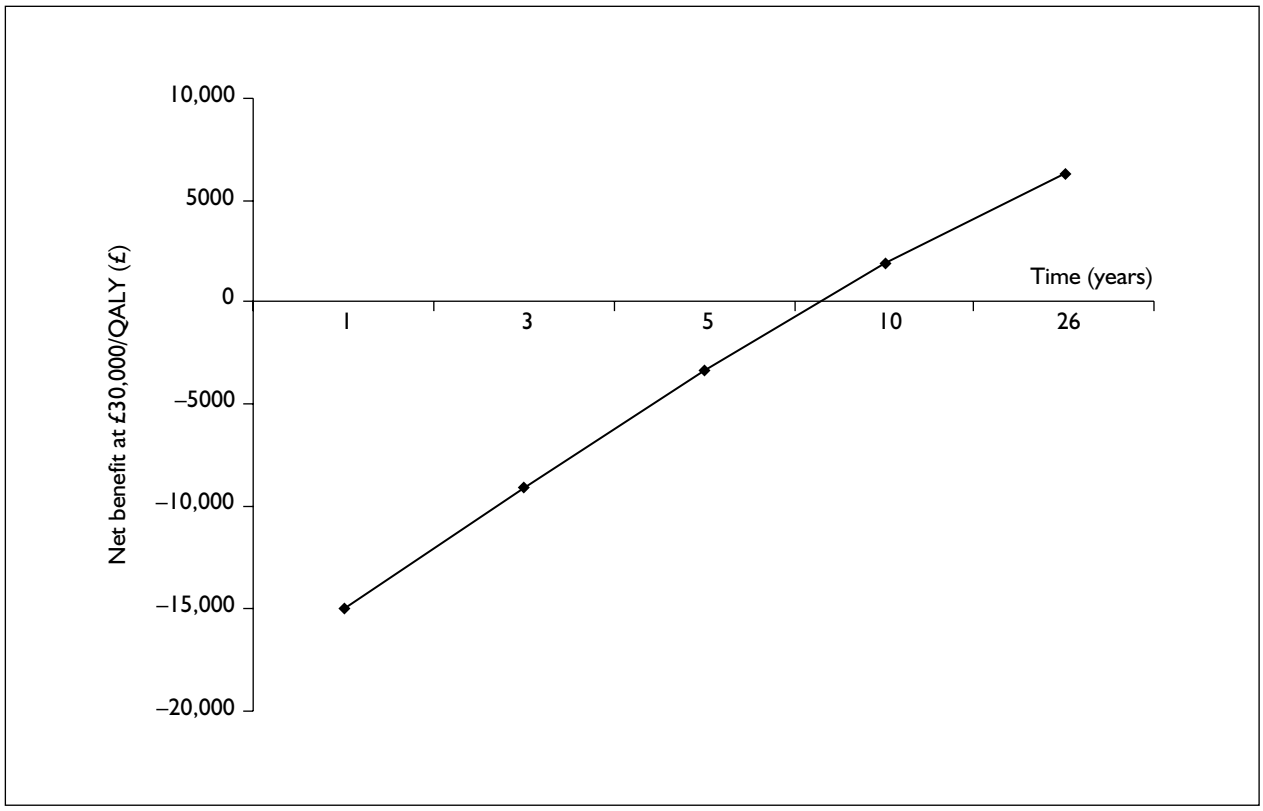

FIGURE 40 *Threshold analysis of time horizon (CRT-D device)*

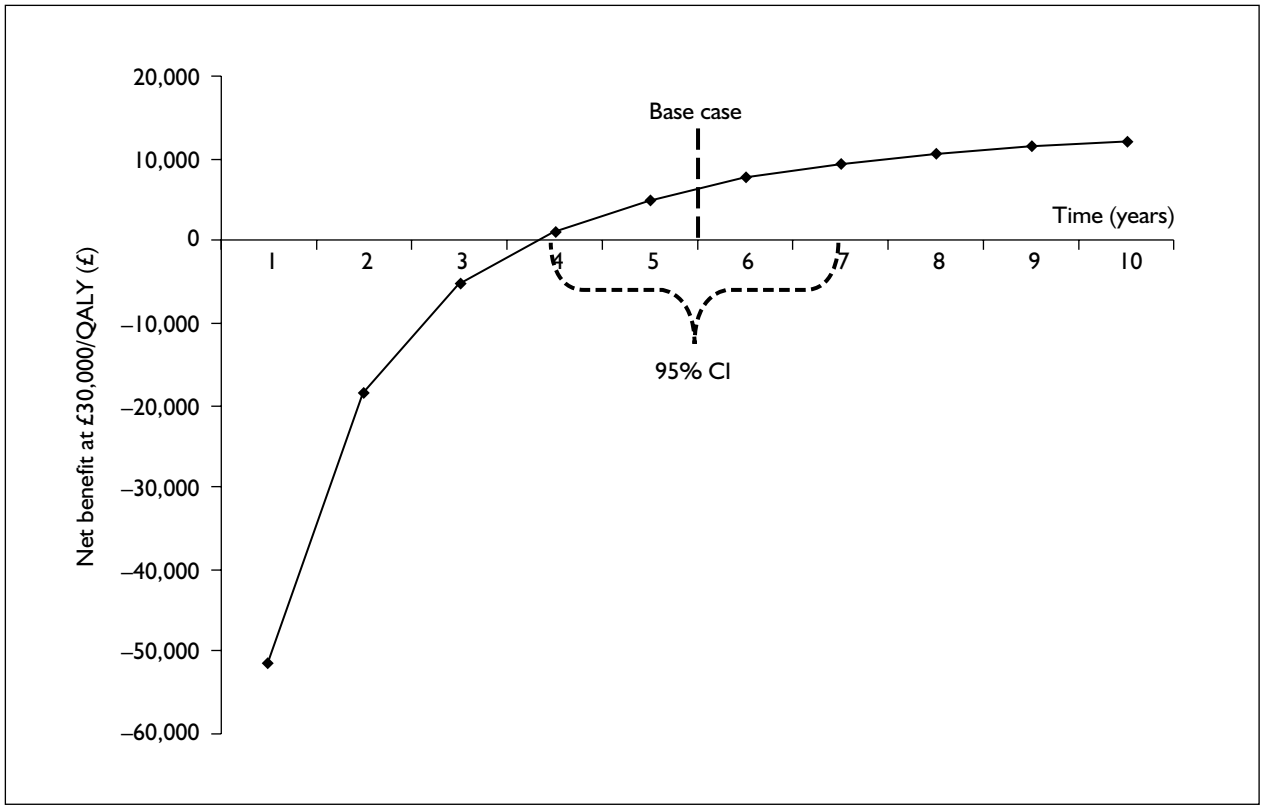

FIGURE 41 *Threshold analysis for CRT-D device lifetime*

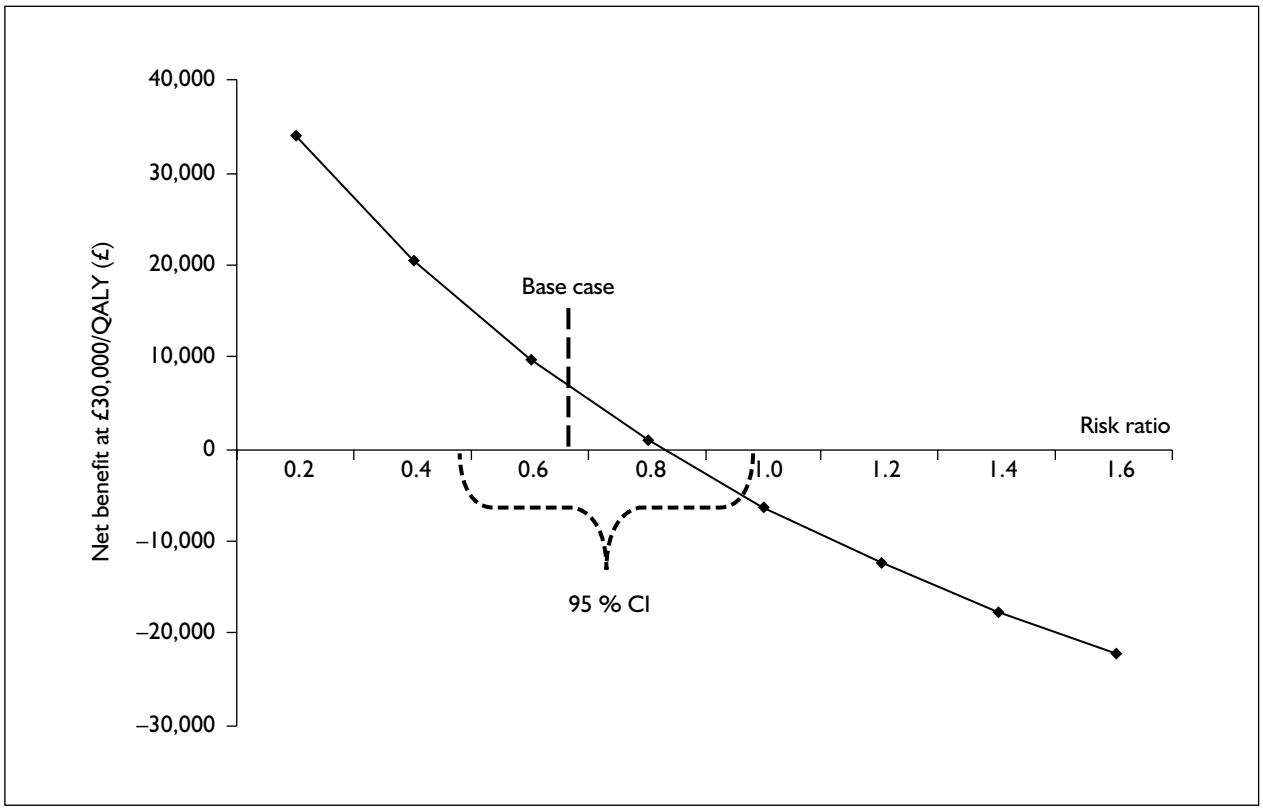

FIGURE 42 *Threshold analysis for risk of death due to worsening HF with a CRT-D device compared with OPT*

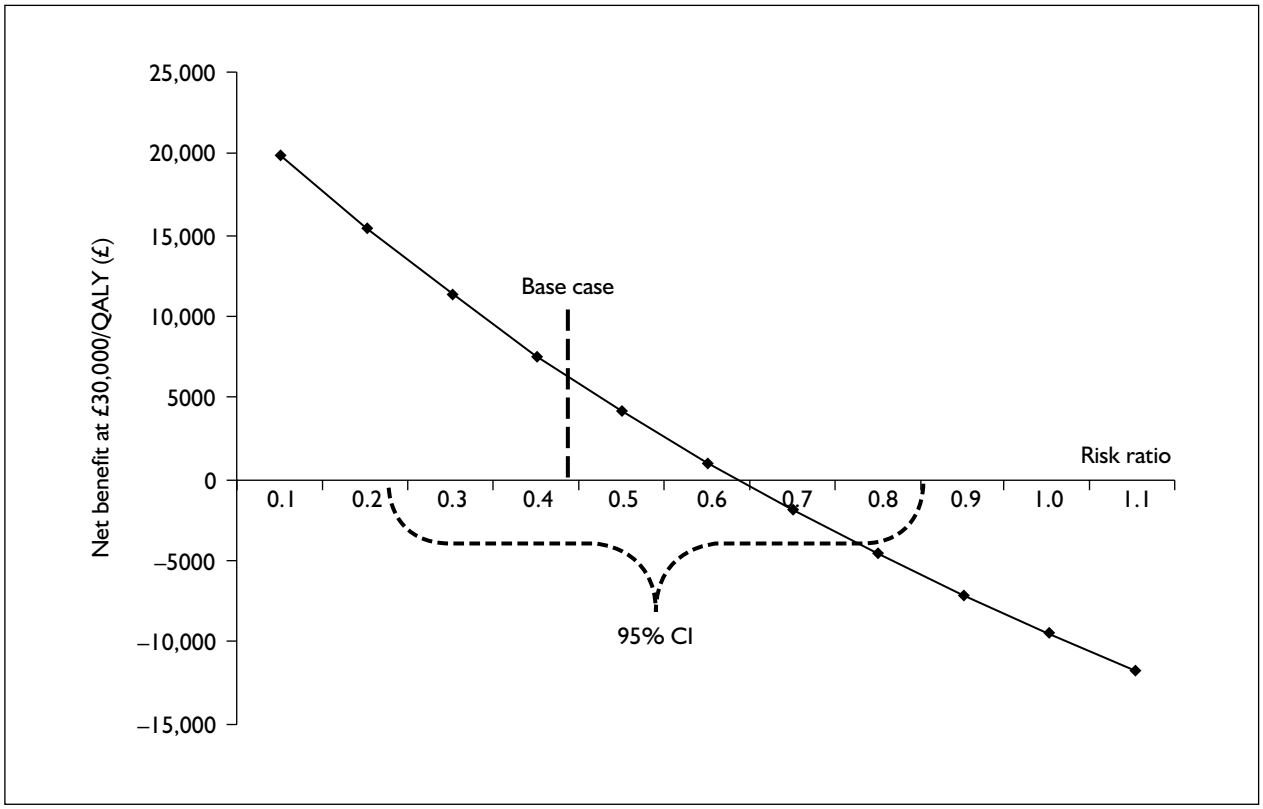

FIGURE 43 *Threshold analysis for risk of sudden death with CRT-D device compared with OPT*

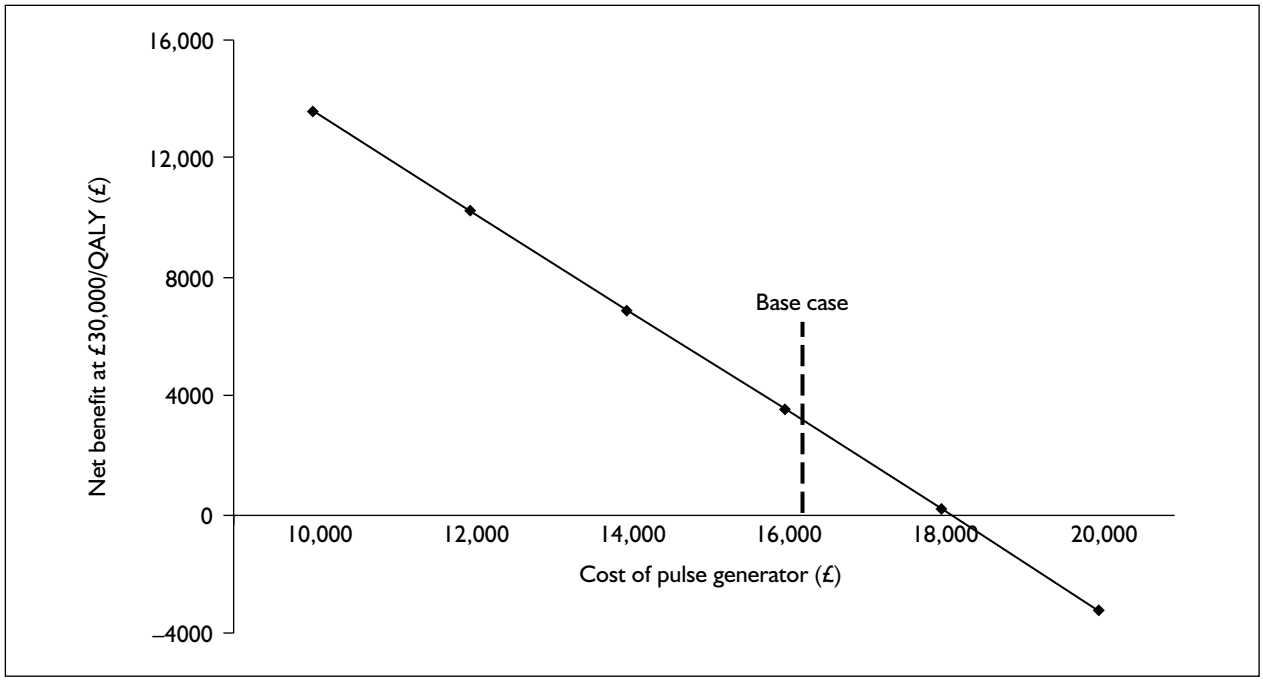

FIGURE 44 *Threshold analysis of CRT-D pulse generator cost*

means that there would have to be at least a 75% reduction in the risk of SCD with CRT-D compared with OPT to be considered cost-effective.

Threshold analysis for CRT-D device (pulse generator) versus OPT cost

Figure 44 shows the threshold analysis for unit cost of a CRT-D pulse generator when compared with OPT. It shows that at a WTP threshold of £30,000/QALY, treatment with CRT-D would be considered cost-ineffective if the device cost were increased to approximately £18,000 from the current cost of £14,391 (as presented in *Table 46*). This means that a price increase of approximately 25% is necessary before CRT-D becomes cost-ineffective.

At a WTP threshold of £20,000/QALY, treatment with a CRT-D device becomes cost-ineffective when the generator price rises above approximately £12,500. This represents a reduction of 13.1% from the current price.

Probabilistic sensitivity analysis

The ranges and distributions used were sampled from the events, utility values and costs shown in Appendix 7.

Outputs from the Monte Carlo simulation are shown graphically (*Figure 45*). For the modelled mixed age cohort these illustrate the ICER values for 1000 simulated trials. Lines representing WTP thresholds of £20,000 and £30,000 per QALY have also been included. The simulation output shows that at £20,000 per QALY CRT-D is cost effective in 24.3% of simulations undertaken and at £30,000 per QALY in 73.2% of simulations undertaken. CRT-D was negatively dominated in 0.3% of simulations (higher incremental costs compared with OPT but lower incremental QALYs).The probabilistic mean ICER is £26,660 (95% CrI £25,470 to £27,850) and the probabilistic median ICER value is £24,174. These values show that the distribution ICERs are heavily skewed (skewness coefficient –13.18).

The CEAC for the comparison of CRT-D with OPT is shown in *Figure 46*. This shows that CRT-D would only be considered cost-effective beyond a WTP threshold of approximately £24,000 per QALY.

Value of information analysis

Patient-level EVPI for CRT-D versus OPT

At a WTP threshold of £30,000, the model predicts that the upper limit of value that could be obtained from acquiring perfect information on all input parameters would be around £917 per patient based on the levels of uncertainty recorded for the initial model parameters (*Figure 47*).

Population-level EVPI for CRT-D versus OPT

Based on an assumed 6300 patients per year in England and Wales receiving CRT, and a decision horizon of 6 years (approximately the average lifetime of a device), the total EVPI at the

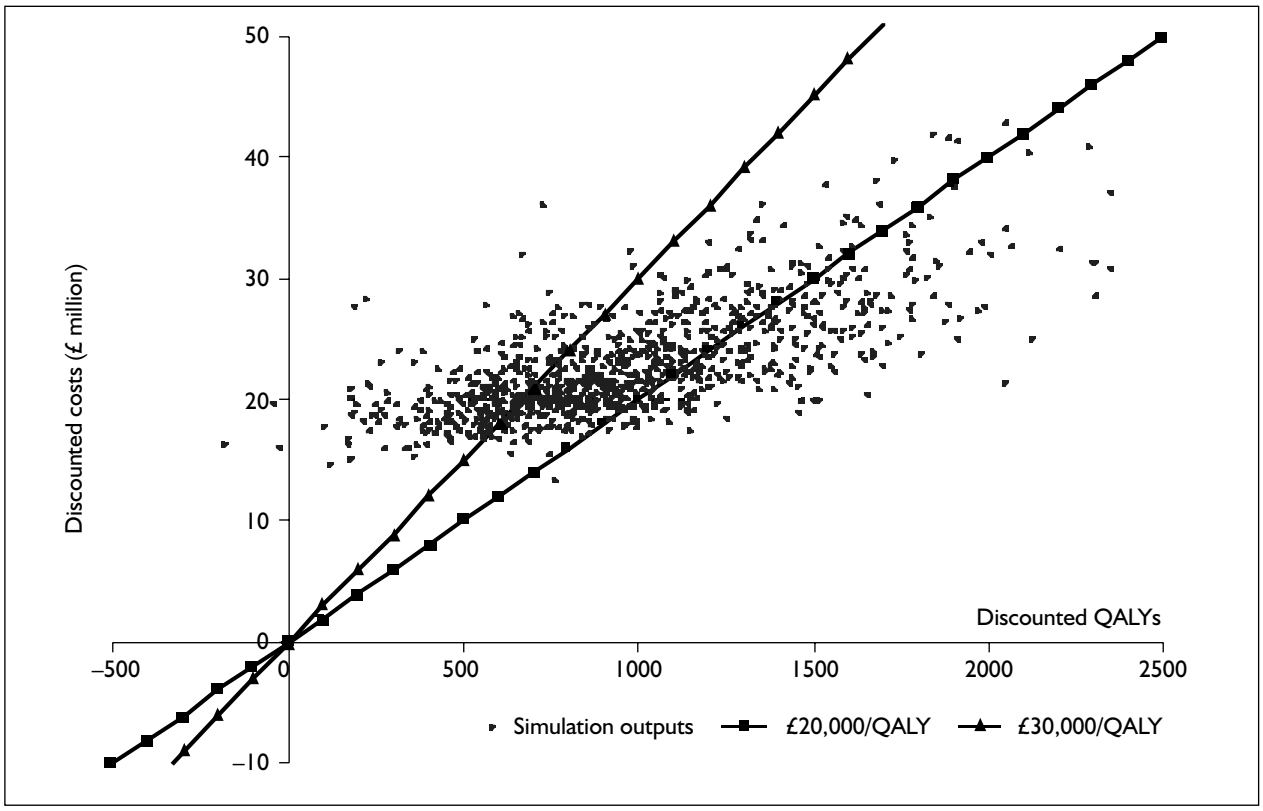

FIGURE 45 *Simulation output (cohort based, 1000 trials) for the cost-effectiveness of CRT-D in comparison with OPT*

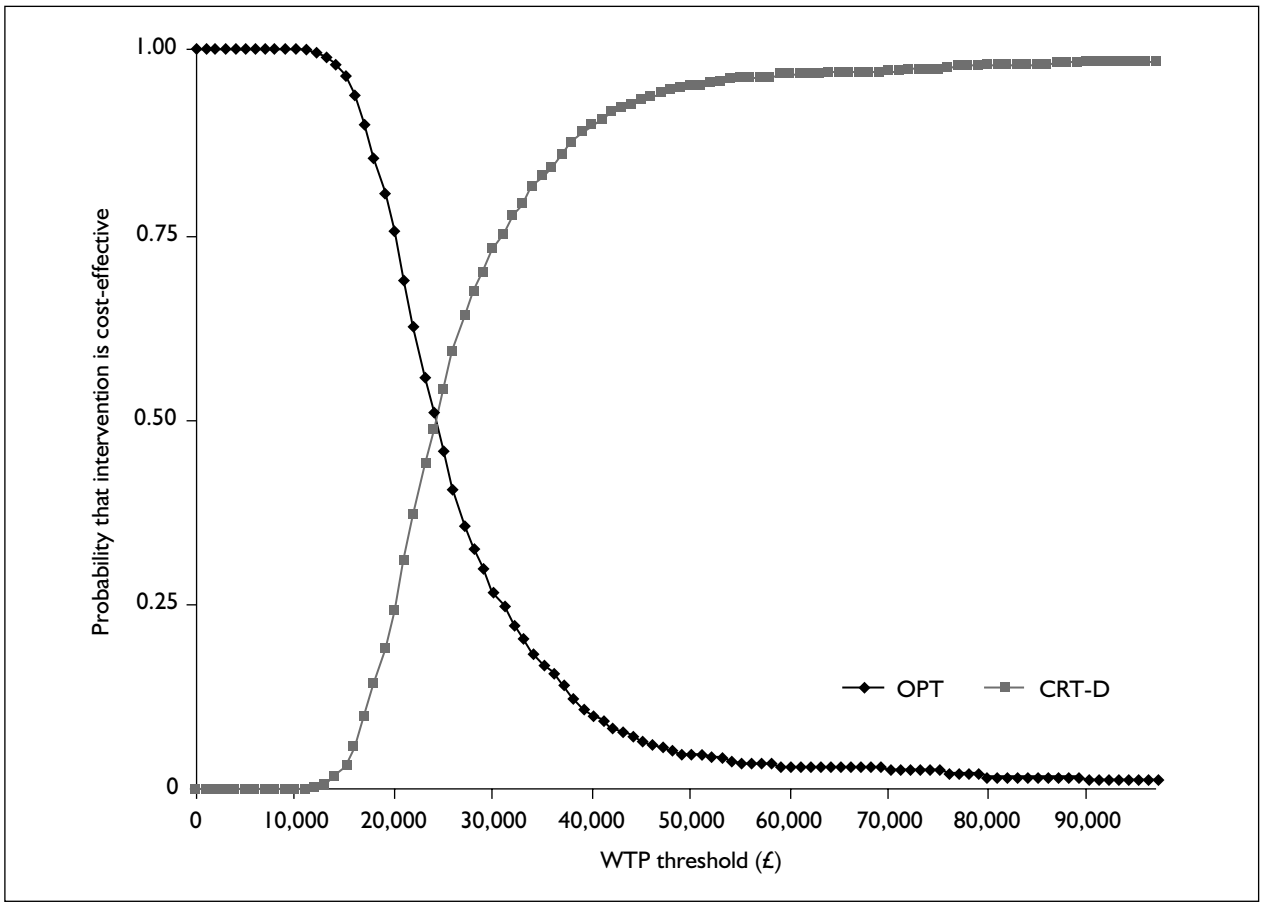

FIGURE 46 *Related probabilities that either CRT-D or OPT is cost-effective at various WTP thresholds*

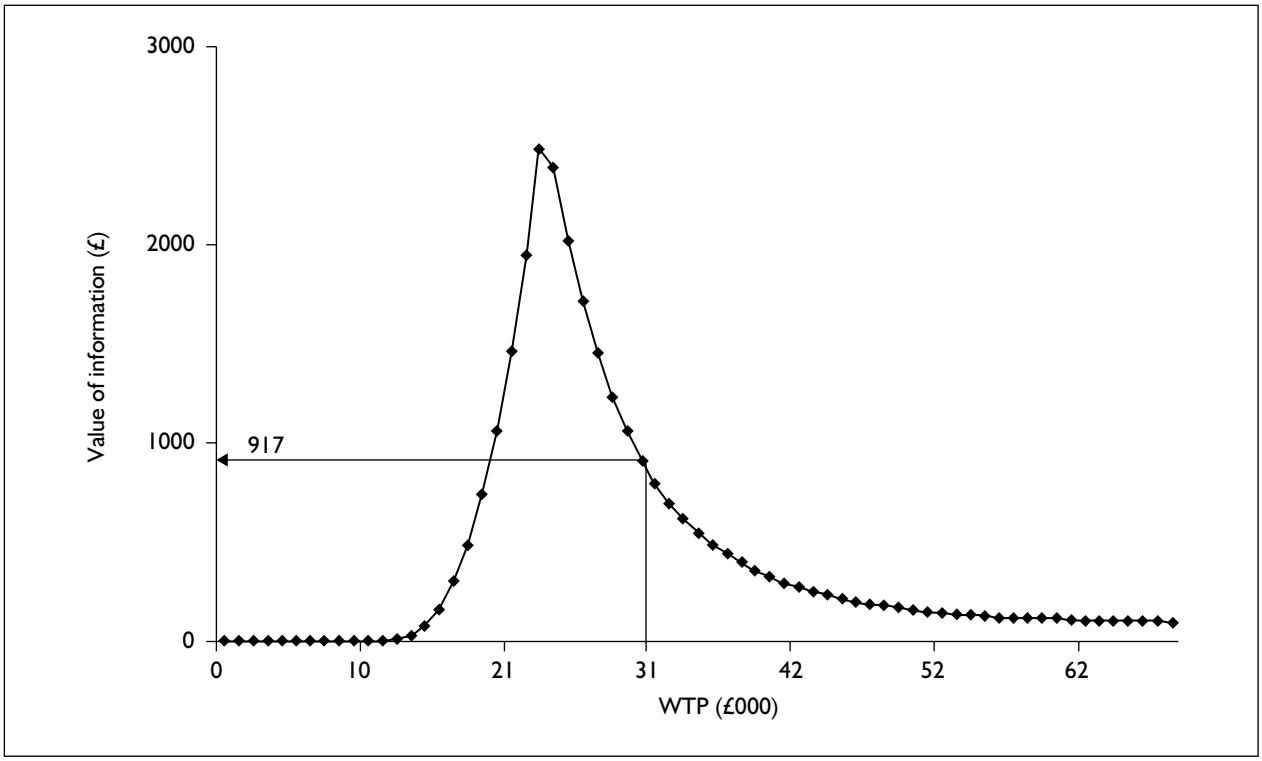

FIGURE 47 *Total EVPI at the patient level (CRT-D versus OPT)*

population level is £31.8 million. The calculation was performed using a WTP threshold of £30,000 per QALY.

The WTP threshold used in the above calculation represents the upper threshold used by NICE in their evaluations of new technologies. Therefore, the value calculated represents an upper bound on the potential benefit of extra research aimed at reducing the uncertainty in the model (*Figure 48*).

The population EVPI in *Figure 48* represents the upper bound on the value of future research on the decision problem. The value of information in this case (£31.8 million) suggests that further research would be beneficial.

Total EVPPI

Further investigation of the value of information was carried out using EVPPI. Results of the analysis for CRT-D versus OPT are shown in *Figure 49*.

These results show that the maximum reduction in decision uncertainty is £17,803,906 for all HRs, £7,210,502 for all survival curves, £19,179,101 for SCD and £2,008,413 for death due to worsening HF. Therefore, further information on these parameters could have a significant impact on decision uncertainty. Further information on transition probabilities, costs and utilities would have a negligible impact on decision uncertainty.

Cost-effectiveness of CRT-D compared with CRT-P

Base case results of cost-effectiveness

Base case results produced by the economic model for different cohort starting ages as well as for the overall mixed age cohort are shown in *Table 69* on a per patient basis. For the mixed age cohort, in comparison with CRT-P the implantation of a CRT-D device provides an extra 0.29 QALYs (106 quality-adjusted days). However, this improvement would cost the NHS £11,689 per person to achieve.

The ICER values generated for CRT-D versus OPT increase with age. There was a slight upward trend in the ICERs for CRT-P versus OPT (*Table 58*) and a more pronounced upward trend in the ICERS for CRT-D versus OPT (*Table 64*). These results combine to produce the values presented above.

Model outputs

Event counts

The event counts produced in *Tables 59* and *65* relating to the CRT-D and CRT-P arms of the model are reproduced in *Table 70*.

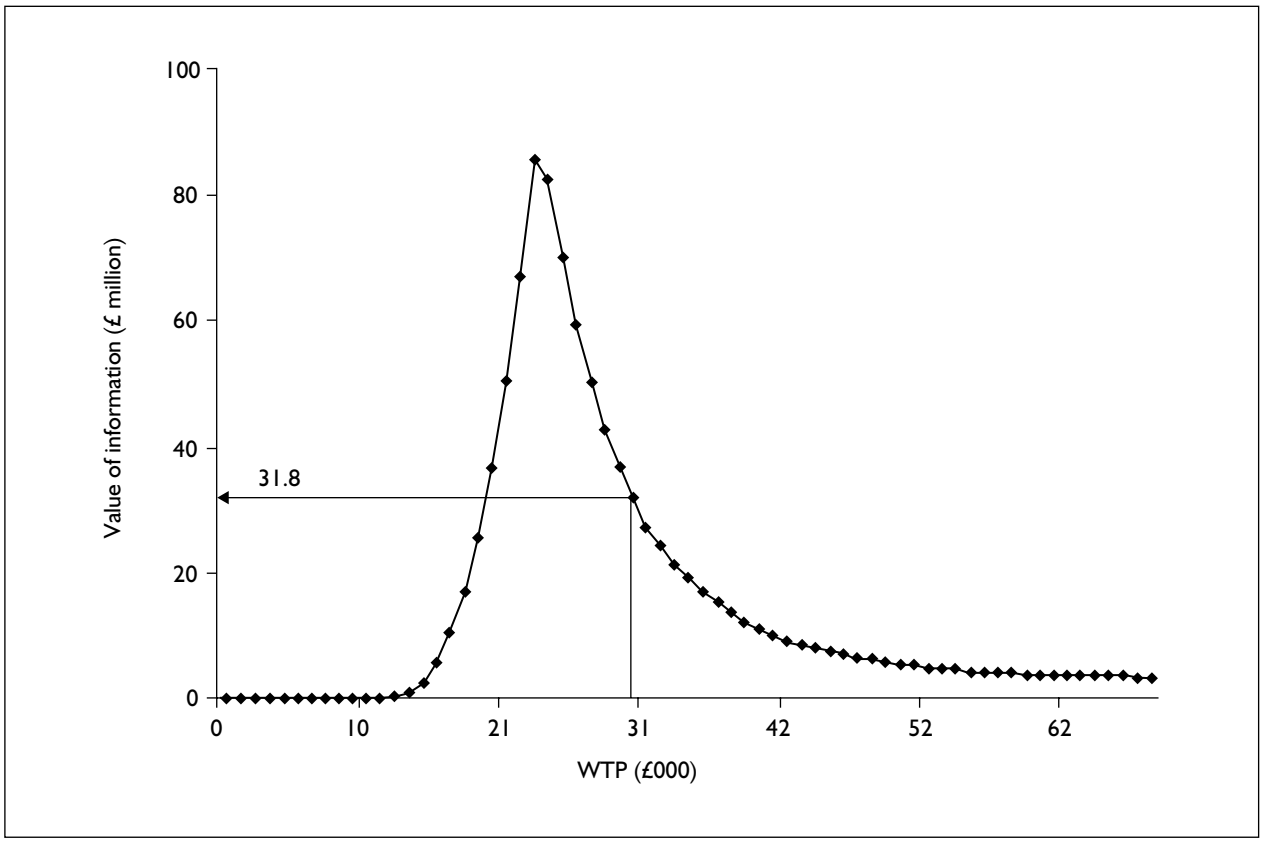

FIGURE 48 *Total EVPI at the population level (CRT-D versus OPT)*

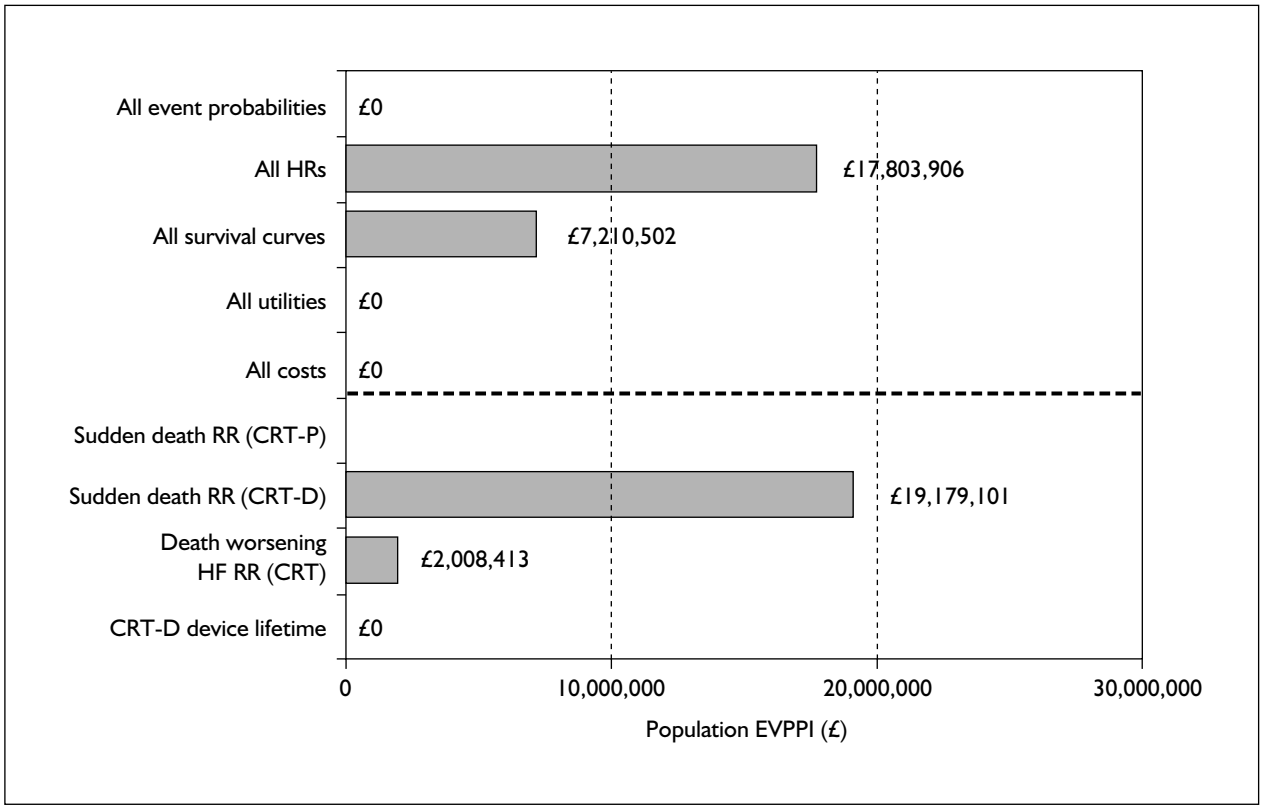

FIGURE 49 *EVPPI for CRT-D versus OPT*

TABLE 69 *Discounted base case cost-effectiveness results per patient for CRT-D compared with CRT-P (lifetime time horizon)*

Start age (years)	CRT-P costs (£)	CRT-P QALYs	CRT-D costs (£)	CRT-D QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
30	34,861	6.70	48,568	7.21	13,707	0.51	26,645
40	34,320	6.59	47,907	7.09	13,587	0.49	27,462
50	32,716	6.27	45,976	6.71	13,260	0.44	29,819
60	28,180	5.33	40,808	5.71	12,627	0.37	34,044
70	22,212	4.07	34,129	4.40	11,917	0.32	36,786
80	17,872	3.13	29,125	3.39	11,254	0.25	44,172
90	15,178	2.53	26,015	2.71	10,837	0.18	59,391
Mixed	**20,997**	**3.80**	**32,687**	**4.09**	**11,689**	**0.29**	**40,160**

TABLE 70 *Patient-relevant outcomes in the model for mixed age cohorts of 1000 people*

	CRT-P + upgrades (%)		CRT-D + upgrades[a] (%)		Difference (%)
	Event likelihood over lifetime	Event rate per 100 patient-years	Event likelihood over lifetime	Event rate per 100 patient-years	
Infection	15.3	2.89	17.1	3.00	+1.8
Lead displacement	10.3	1.89	11.6	1.98	+1.3
Total routine device changes	49.3	NA	68.2	NA	+18.9
CRT-P	19.3	NA	0.0	NA	NA
CRT-D	28.5	NA	67.5	NA	+39.0
ICD	1.5	NA	0.6	NA	–0.8
Device upgrades	37.4	NA	0.7	NA	–36.7
CRT-D	35.9	NA	0.0	NA	NA
ICD	1.6	NA	0.6	NA	–0.8
Serious arrhythmic event	37.4	8.16	0.7	0.11	–36.7
Surgical complication	21.9	4.29	20.7	3.71	–1.2
Surgical failure	5.8	1.03	2.7	0.43	–3.1
Heart transplant	0.3	0.04	0.3	0.04	0.0
Hospitalisation as a result of HF	1.82	31.7	1.98	31.7	+0.16

NA, not applicable.

TABLE 71 *Additional life for people in the CRT-D arm compared with people in the CRT-P arm of the PenTAG model*

Start age (years)	25% centile (years)	Median survival (years)	75% centile (years)	Mean survival (years)	Proportional increase in overall survival (%)
30	0.69	1.15	1.54	1.1	12.7
40	0.69	1.15	1.46	1.0	12.8
50	0.69	1.08	0.92	0.8	12.3
60	0.62	0.69	1.00	0.7	9.7
70	0.39	0.39	0.77	0.5	7.1
80	0.23	0.46	0.46	0.4	12.2
90	0.15	0.23	0.46	0.3	8.6
Mixed	**0.23**	**0.46**	**0.69**	**0.4**	**10.0**

TABLE 72 *Overall state occupancies per person in the economic model for mixed age cohorts of 1000 people (excluding death)*

	CRT-P + upgrades (% of overall life)	CRT-D + upgrades (% of overall life)
Implant surgery	1.8	1.2
Postoperative complications	0.3	0.3
Routine upgrades	0.7	0.8
Stable with therapy	94.4	94.9
Lead displacement	0.1	0.1
Infections	0.2	0.2
HF hospitalisation	2.4	2.4

The keys are a large increase in routine device changes, a large reduction in the number of device upgrades and an increase in the number of arrhythmic events.

Given that people with CRT-D can be expected to live longer (*Table 71*), and that CRT-D devices have a shorter average lifetime than CRT-P devices, the increased number of routine changes is not surprising. The cost of a CRT-D device change is approximately four times that of a CRT-P device (mean implantation costs: CRT-P £3,809, CRT-D £16,001).

Survival

Table 71 shows the survival gains for people with a CRT-D device compared with a CRT-P device.

On average, younger people (those ⩽60 years old) given a CRT-D device can expect to live longer than those implanted with a CRT-P device, Older people in the same circumstances (in terms of percent of overall life) do not have the same survival gain. Overall people with a CRT-D device can expect to live 0.4 years longer than a person with a CRT-P device. The PenTAG systematic review reported no significant gain in life based on a single direct comparison. The indirect comparison produced by the PenTAG model shows a slight reduction in mortality risk with a CRT-D device (RR 0.897, 95% CrI 0.892 to 0.902).

State occupancy

The state occupancies for each of the CRT-P and CRT-D arms of the model are presented in *Table 72*. Meta-states have been created for the purposes of presentation. All forms of death have again been excluded from the table. Whereas people with a CRT-D live longer than people with a CRT-P, the proportion of time that they spend in each meta-state is almost identical.

Incremental analysis for non-reference case scenarios with justification

In order to aid the comparison of the results produced by PenTAG with other models, the time horizon was fixed to 5 years and the outputs that impact on cost-effectiveness were recorded. These values are shown in Appendix 7.

Sensitivity analysis

One-way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied independently of all other model inputs, had the greatest impact on the incremental cost-effectiveness of CRT-D compared with CRT-P.

The results of the analyses have been expressed graphically, showing the absolute net benefit associated with each new value based on a WTP threshold of £30,000 per QALY. Because of the large numbers of parameters used in the construction of the model, the results have been presented as separate graphs for structural parameters (*Figure 50*), event-related probabilities (*Figure 51*), HRs and survival analysis (*Figure 52*), utilities (*Figure 53*) and costs (*Figure 54*). Baseline net benefit is again shown by a vertical line.

Bars to the right of the baseline value represent an increase in incremental net benefit with CRT-D compared with CRT-P, whereas those to the left show a reduction in incremental net benefit. The baseline ICER is below £30,000 per QALY and so a net benefit reduction of 100% is necessary for an intervention to be cost-ineffective. Such a reduction changes the net benefit from positive to negative.

In the analysis of the effect of changes in input parameters on the cost-effectiveness of CRT-D compared with CRT-P, the model appears particularly sensitive to:

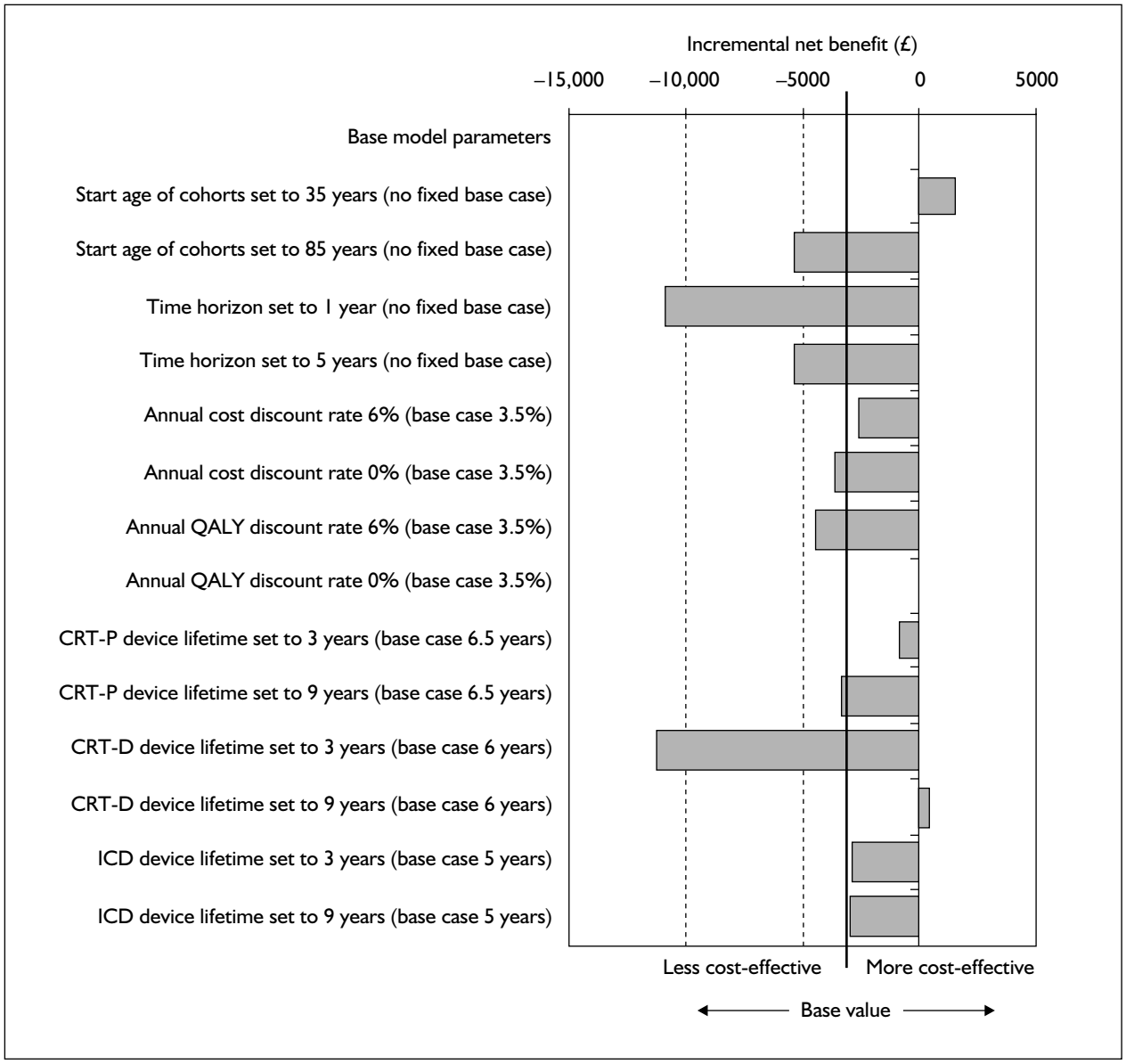

FIGURE 50 *One-way sensitivity analysis for structural inputs in the economic model: absolute net benefit of CRT-D compared with CRT-P at a WTP of £30,000/QALY*

1. *Structural parameters*:
   (a) the time horizon of the model
   (b) the discount rate applied to health benefits
   (c) the lifetimes of both types of CRT device
2. *Event probabilities*:
   (a) probability of an arrhythmic event with CRT-P
   (b) probability of an infection with CRT-P
3. *HRs and survival analysis*:
   (a) risk of sudden death with both types of CRT device
   (b) risk of death as a result of worsening HF with either CRT device.

The model appears relatively stable to changes in cost and utility parameters. Only the costs associated with initial device implantation (both CRT-D and CRT-P) had any significant effect on incremental net benefit.

Threshold analysis

CRT-P device lifetime

Threshold analysis for the expected lifetime of a CRT-P device shows that at a WTP threshold of £30,000 per QALY, treatment with CRT-D as opposed to CRT becomes cost effective when the parameter value falls below approximately 2.5 years (*Figure 55*). Currently, the expected lifetime of a CRT-P device is 6.5 years. Therefore, CRT-D would be considered cost-effective if CRT-P devices were changed approximately 2.5 times as often as they are now. At a WTP threshold of

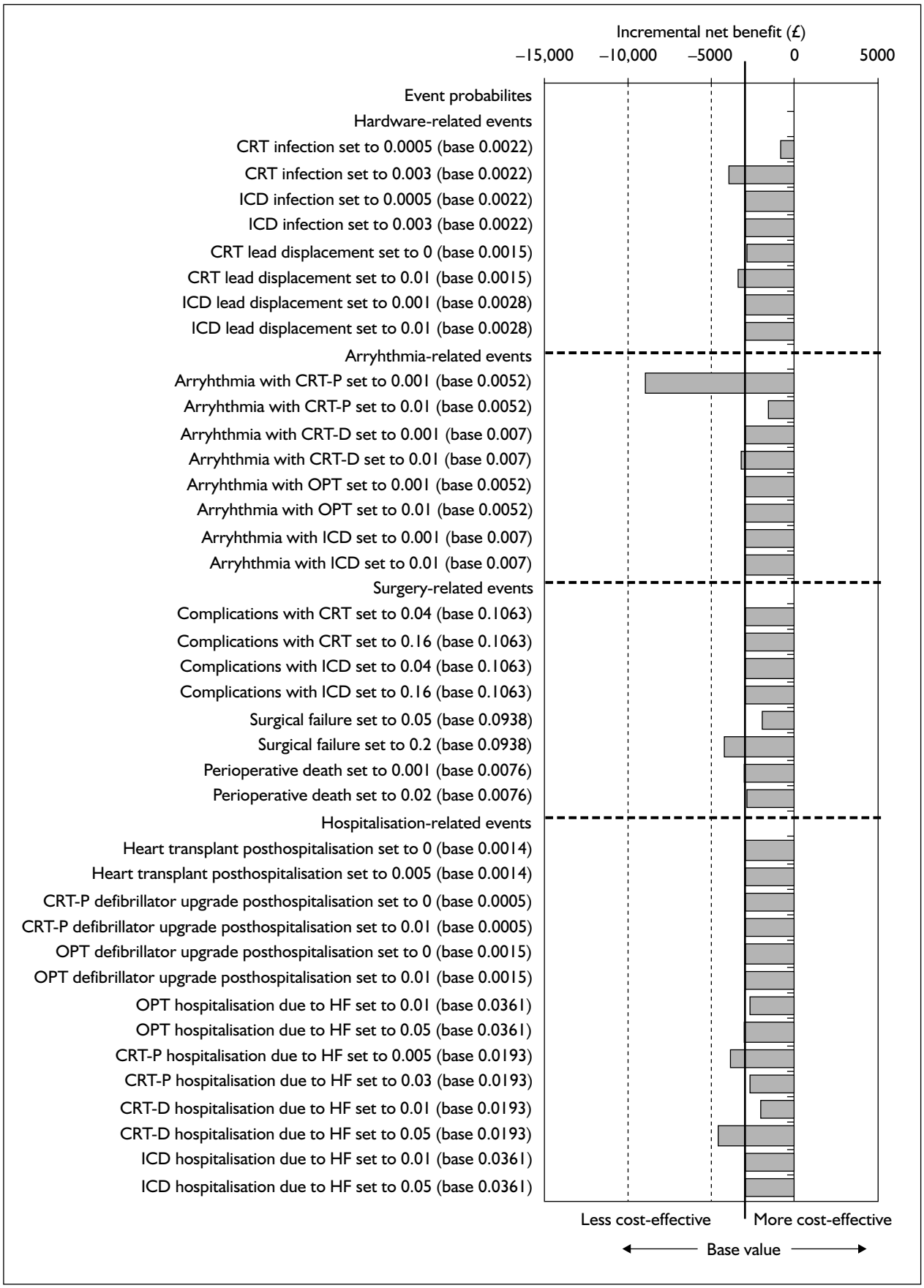

FIGURE 51 *One-way sensitivity analysis for event inputs in the economic model: absolute net benefit of CRT-D compared with CRT-P at a WTP of £30,000/QALY*

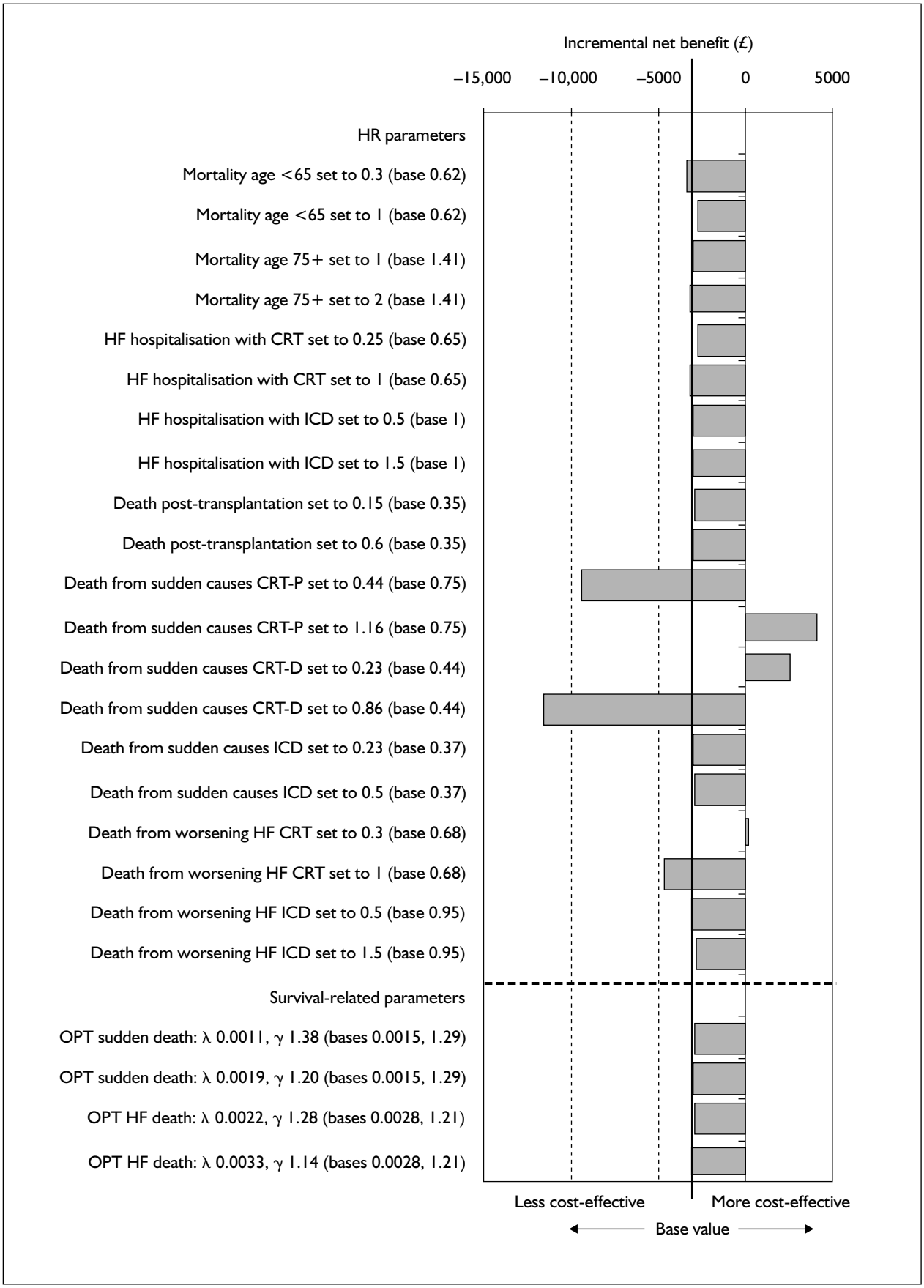

FIGURE 52 *One-way sensitivity analysis for HR and survival inputs in the economic model: absolute net benefit of CRT-D compared with CRT-P at a WTP of £30,000/QALY*

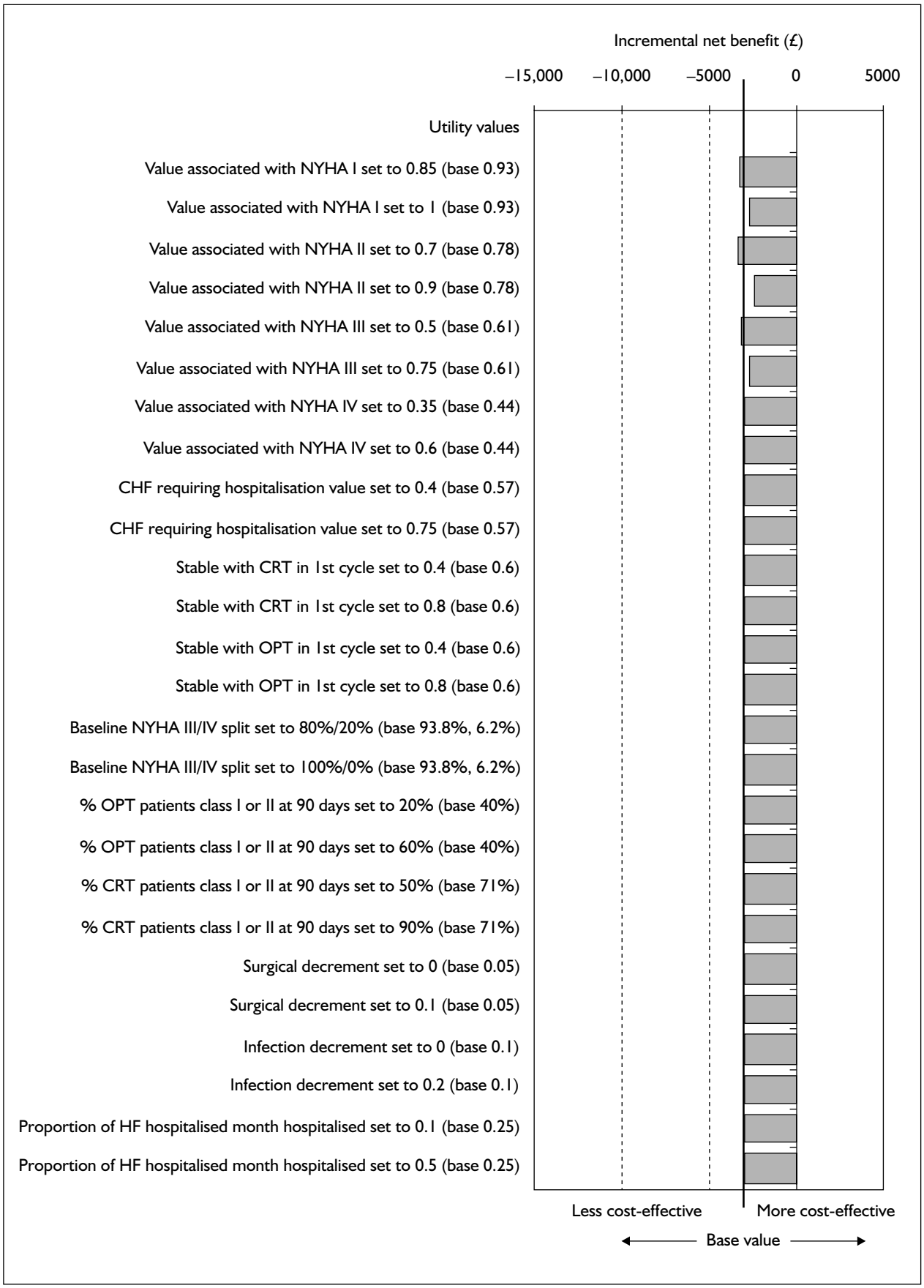

FIGURE 53 *One-way sensitivity analysis for utility inputs in the economic model: % change in incremental net benefit of CRT-D compared with CRT-P at a WTP of £30,000/QALY*

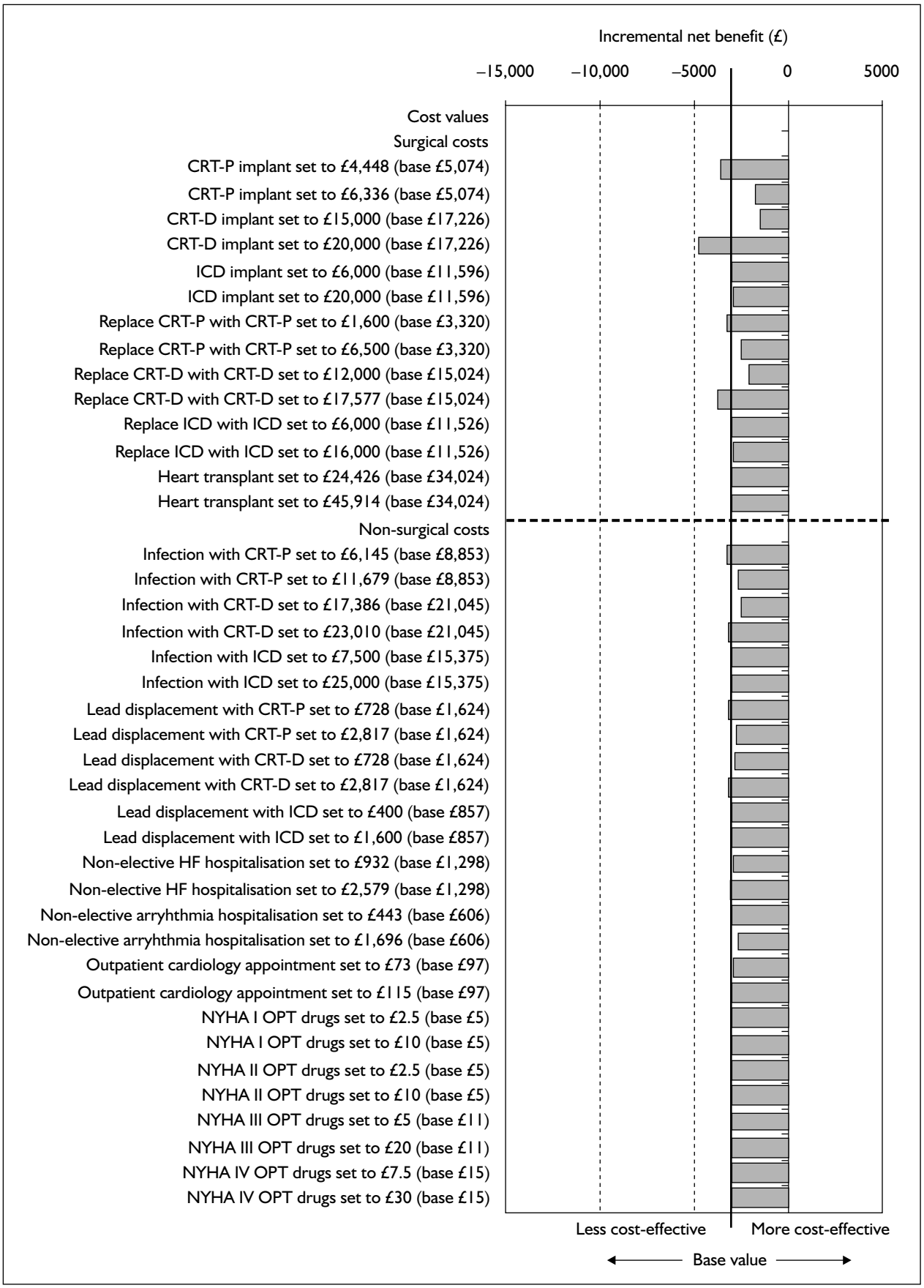

FIGURE 54 *One-way sensitivity analysis for cost inputs in the economic model: absolute net benefit of CRT-D compared with CRT-P at a WTP of £30,000/QALY*

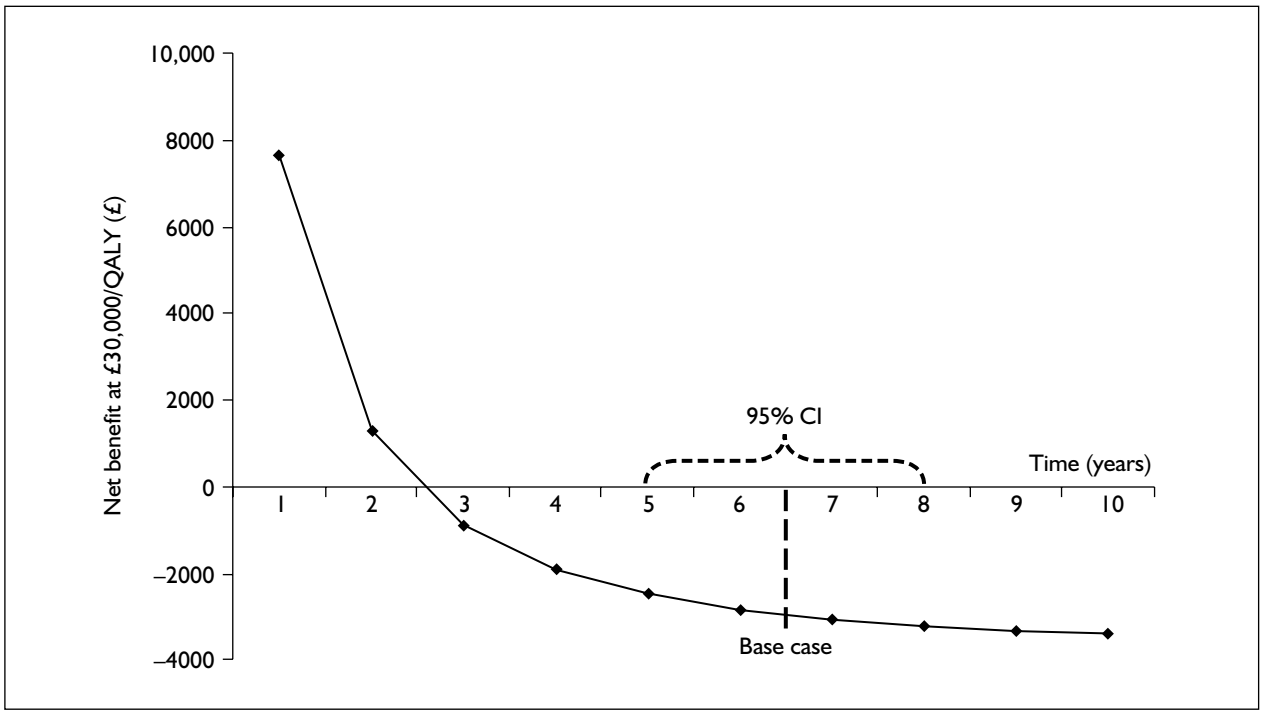

FIGURE 55 *Threshold analysis for CRT-P device lifetime (CRT-D compared with CRT-P)*

£20,000 per QALY, the expected lifetime of a CRT-P device would have to be approximately 1.75 years before CRT-D was considered cost-effective.

CRT-D device lifetime

Threshold analysis for the expected lifetime of a CRT-D device shows that at a WTP threshold of £30,000 per QALY, treatment with CRT-D as opposed to CRT-P becomes cost-effective when the parameter value goes beyond approximately 8 years (*Figure 56*). Currently, the expected lifetime of a CRT-D device is 5.5 years. At a WTP threshold of £20,000 per QALY, there is no realistic value for the expected CRT-D device lifetime that produces a positive net benefit value and therefore changes to CRT-D device lifetime can never make the technology look cost-effective compared with CRT-P.

Relative risk of sudden death

The RR values for each of the devices used to parameterise the model vary, therefore it is necessary to change both in order to perform a threshold analysis.

Changes to CRT-P risk ratio

Threshold analysis for the risk of SCD in people initially implanted with a CRT-D device compared with those initially implanted with a CRT-P device shows that at baseline people with a CRT-P have an RR of 0.75 and people with a CRT-D have an RR of 0.44. At a WTP threshold of £30,000 using baseline values, CRT-D treatment is cost-ineffective. If the RR of SCD with a CRT-P increases to approximately 0.9, then CRT-D becomes cost-effective. If the WTP threshold is reduced to £20,000, then the RR of SCD with a CRT-P would need to increase to approximately 1.35 before the use of CRT-D became cost-effective (*Figure 57*).

Changes to CRT-D risk ratio

A similar analysis was performed where the parameter value corresponding to the risk of sudden death with a CRT-D device was changed (*Figure 58*). This shows that at a WTP threshold of £30,000 per QALY in devices containing a defibrillator, the RR of sudden death compared with CRT-P must be reduced to at least 0.32 in order for the treatment to be considered cost-effective. This confirms the required risk difference between the two devices highlighted by the analysis of changes to the risk of death with a CRT-P device. At a WTP threshold of £20,000 per QALY, the parameter value would have to be less than approximately 0.1 for the treatment to be considered cost-effective.

Threshold analysis for CRT-D device (pulse generator) versus CRT-P cost

Figure 59 shows the threshold analysis for unit cost of a CRT-D pulse generator compared with CRT-P. It shows that at a WTP threshold of £30,000 per

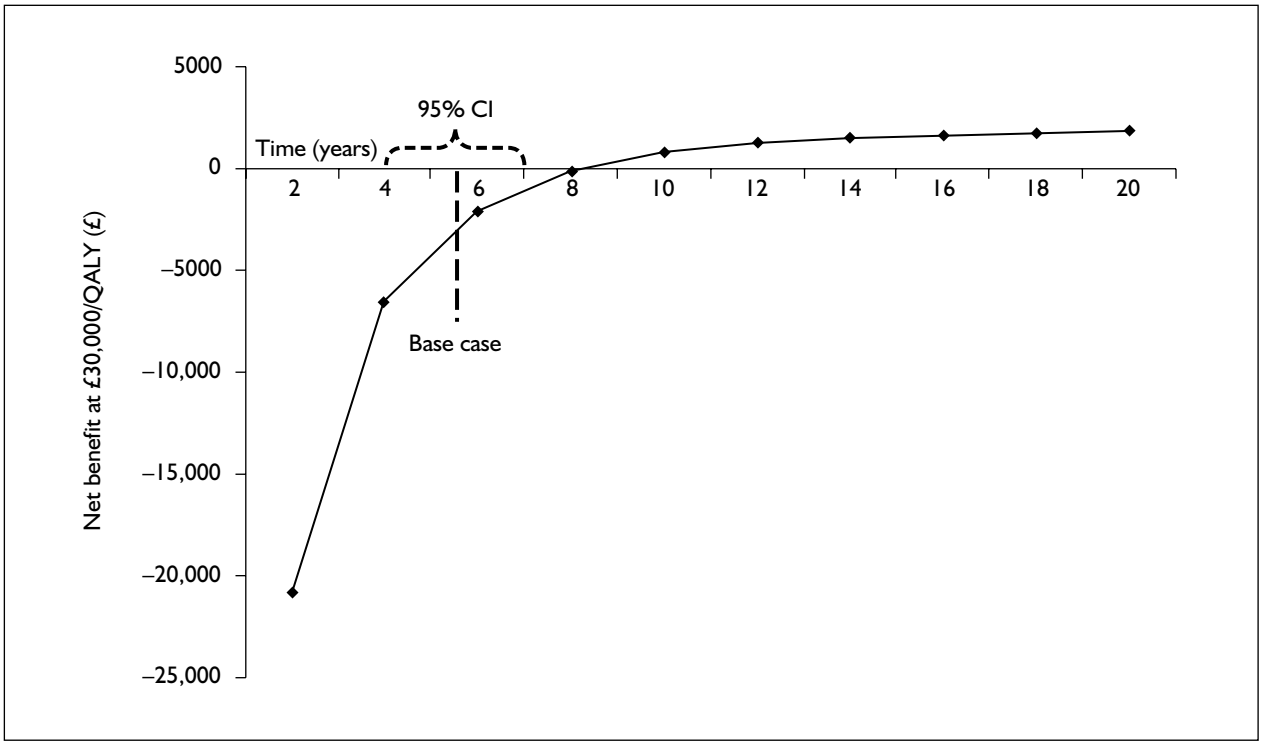

FIGURE 56 *Threshold analysis for CRT-D device lifetime (CRT-D compared with CRT-P)*

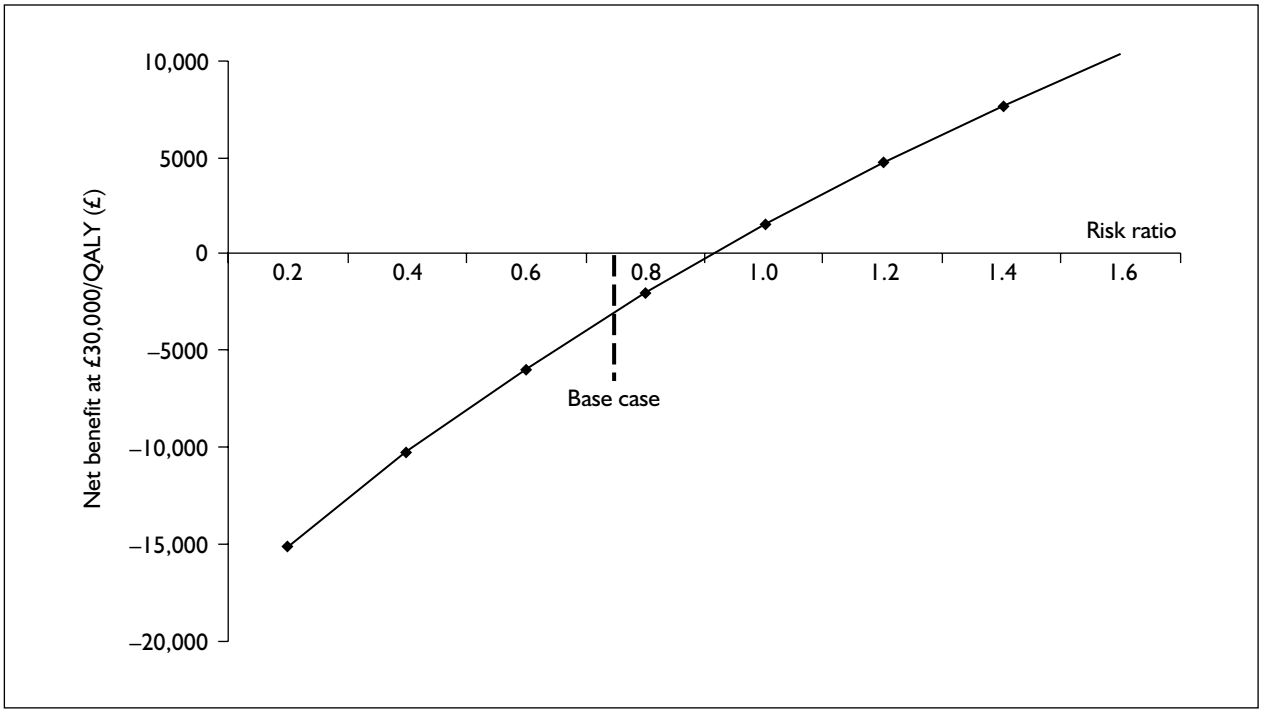

FIGURE 57 *Threshold analysis for risk of sudden death with CRT-P device (CRT-D compared with CRT-P)*

QALY, treatment with CRT-D would be considered cost-effective if the device cost were reduced to approximately £11,500 from the current cost of £14,391 (as presented in *Table 46*). This means that a price reduction of approximately 20% is necessary before CRT-D becomes cost-effective. At a WTP threshold of £20,000 per QALY, generator costs would have to fall to approximately £9,000 (ca 38% reduction in current price) for the device to be considered cost-effective.

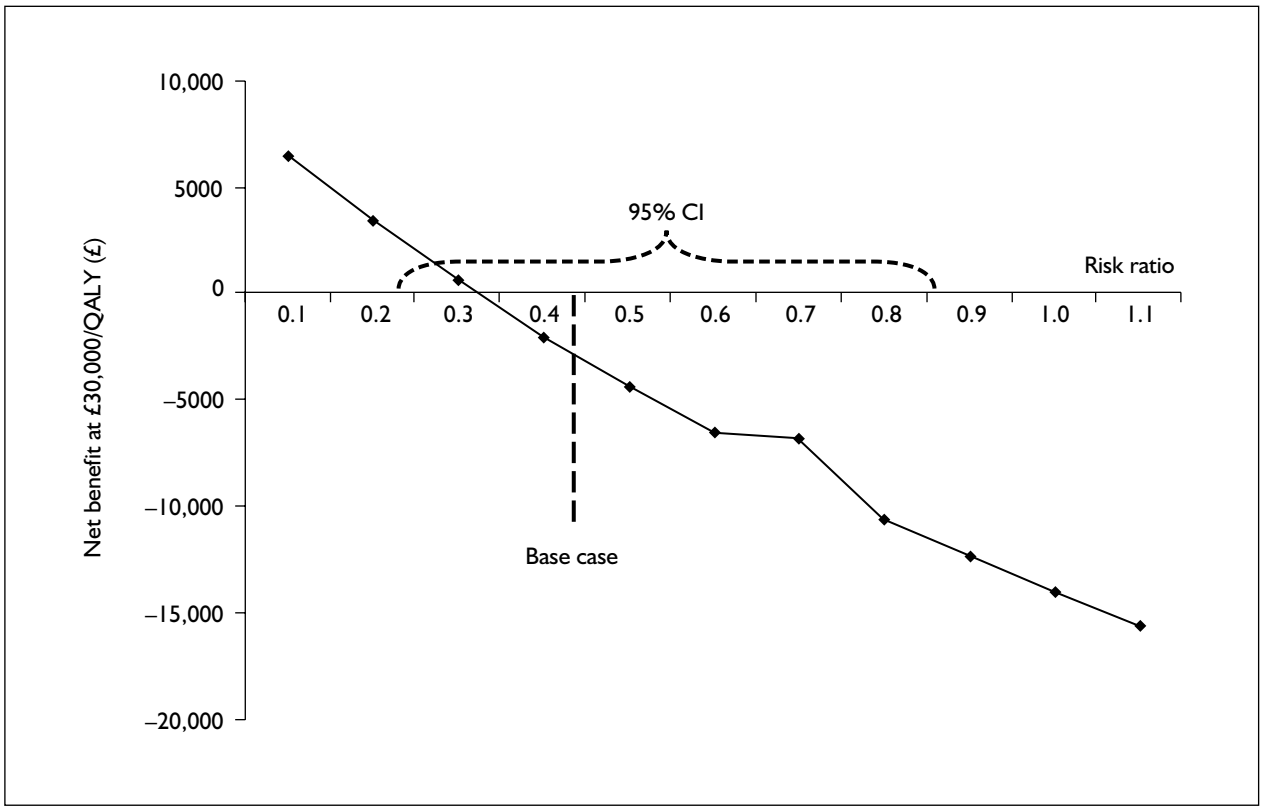

FIGURE 58 *Threshold analysis for RR of sudden death with CRT-D device (CRT-D compared with CRT-P)*

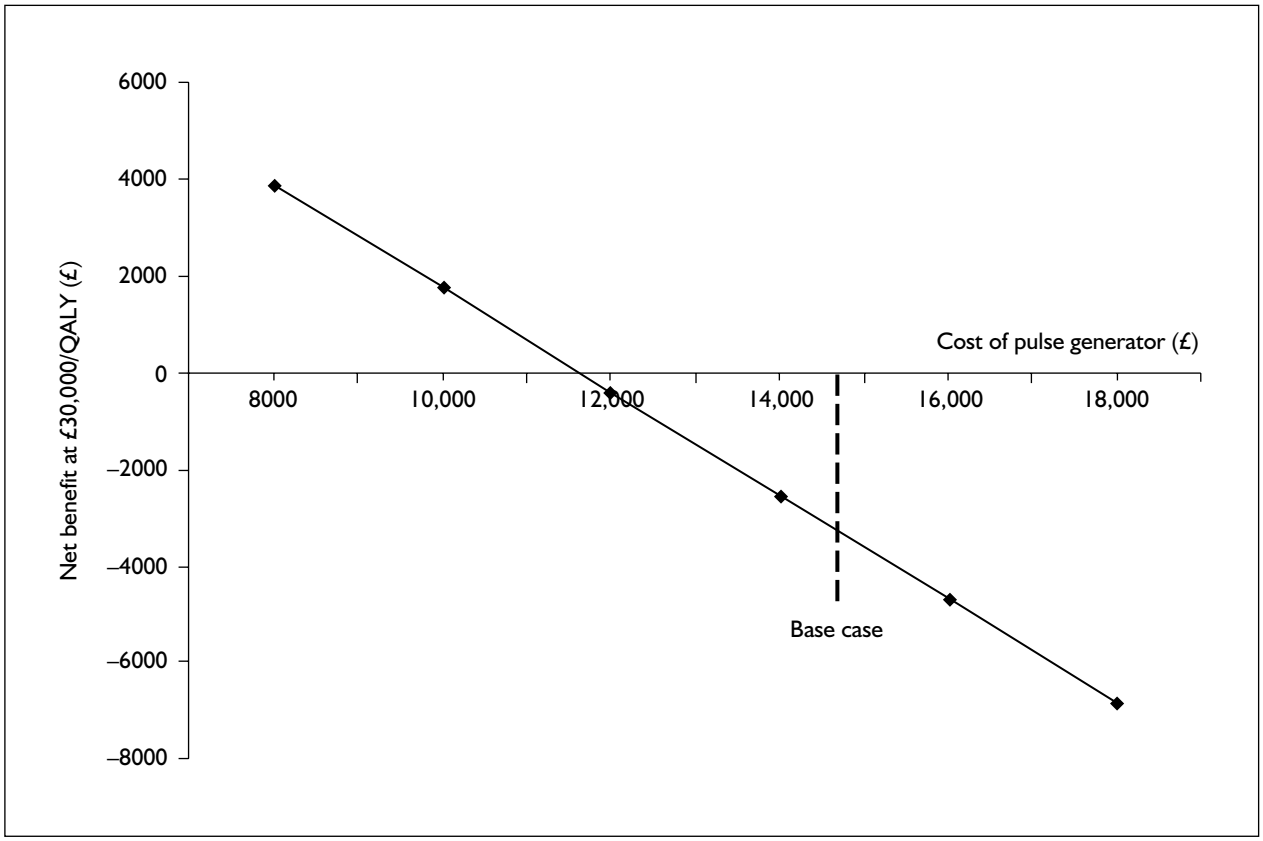

FIGURE 59 *Threshold analysis CRT-D pulse generator versus CRT-P cost*

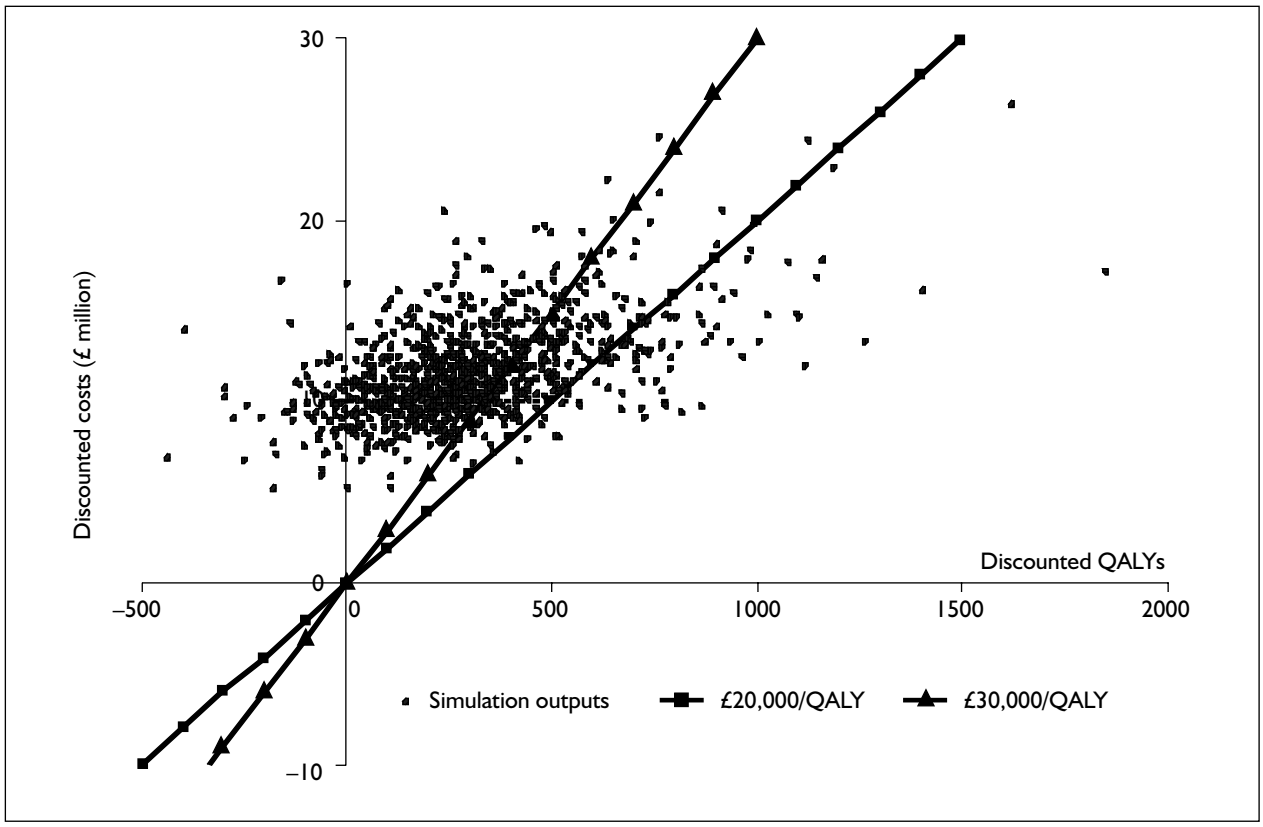

FIGURE 60 *Simulation output (cohort based, 1000 trials) for the cost-effectiveness of CRT-D in comparison with CRT-P*

Probabilistic sensitivity analysis

There is little direct evidence comparing the two interventions, therefore results are derived based on the results of each device (CRT-D and CRT-P) against a common comparator.

Direct comparison of CRT-D versus CRT-P

Outputs from the Monte Carlo simulation are shown graphically in *Figure 60*. For the modelled mixed age cohort these illustrate the ICER values for 1000 simulated trials. The simulation output shows that at £20,000 per QALY, CRT-D is cost-effective in 7.5% of simulations undertaken, and at £30,000 per QALY in 26.3% of simulations undertaken. However, it is important to note that CRT-P dominated CRT-D in 7.8% of all simulation runs. The probabilistic mean ICER is £54,486 (95% CrI £7864 to £101,108) and the probabilistic median ICER value is £37,994. The CEAC corresponding to the comparison of CRT-D to CRT-P is shown in *Figure 61*. This shows that CRT-D would only be cost-effective beyond a WTP threshold of approximately £42,000 per QALY.

Comparison of CRT-D versus CRT-P versus OPT

In this instance, the initial treatment decision (does a patient receive either type of CRT device or continue receiving OPT) is modelled and the outputs (incremental costs and QALYs) refer to the cost-effectiveness of one of these three decisions compared with another.

In situations where there are mutually exclusive treatment options, a common method, proposed by Fenwick and colleagues[132] and Briggs and colleagues,[137] is to construct a cost-effectiveness frontier (CEAF) and to use this to assess the probability of cost-effectiveness of each WTP level. CEAFs represent the efficient points from among the treatment choices. *Figure 62* shows the CEAF produced when comparing the cost-effectiveness of CRT-D with CRT-P or OPT. This shows that at a WTP threshold of £20,000 per QALY, there is a 63% probability that CRT-P offers maximum expected net benefit. At a WTP threshold of £30,000 per QALY, there is a 68% probability that CRT-P offers the maximum expected net benefit. The WTP threshold would have to increase to approximately £40,000 per QALY before CRT-D would provide the highest expected net benefit (although the likelihood of being cost-effective is only 45.6%).

Value of information analysis

For reasons of clarity, only results for the direct comparison of CRT-D with CRT-P have been

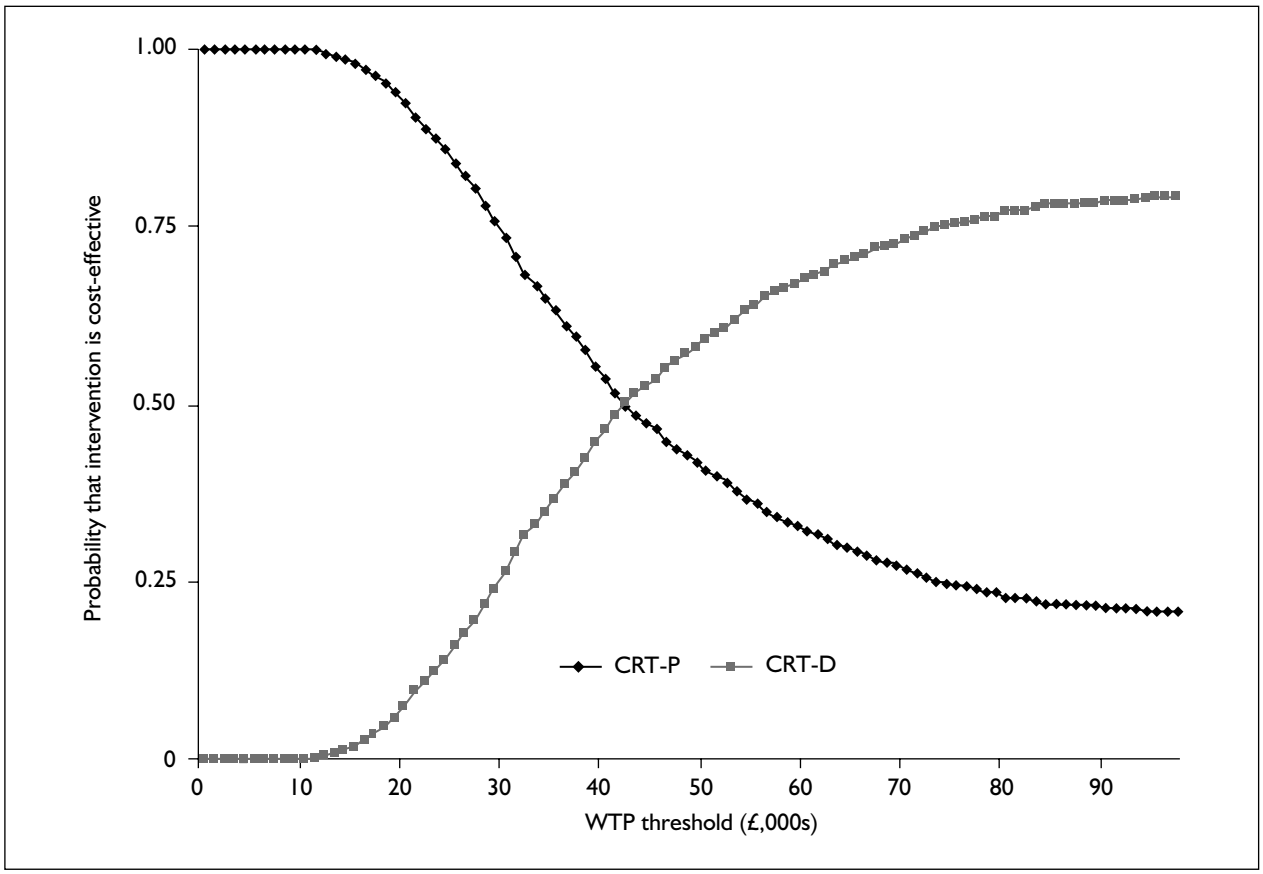

FIGURE 61 *Related probabilities that either CRT-P or CRT-D is cost-effective at various WTP thresholds*

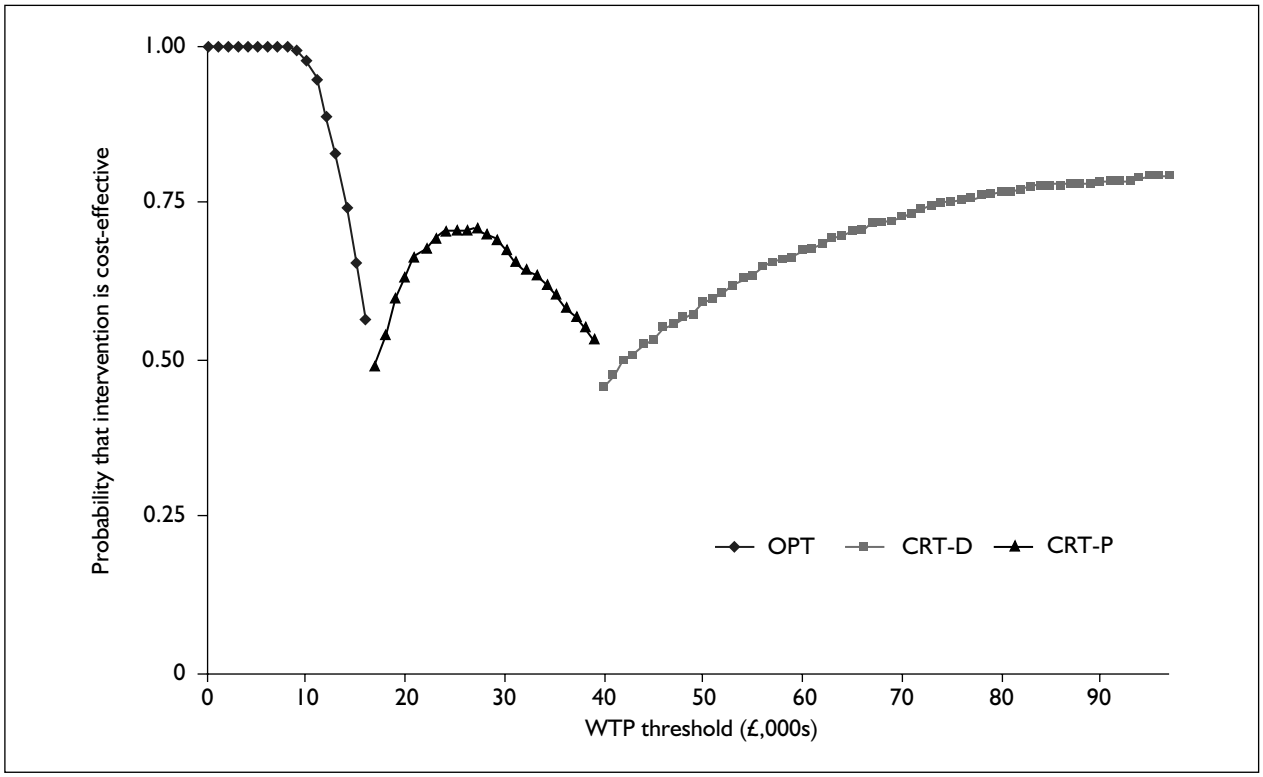

FIGURE 62 *Cost-effectiveness frontier for the decision concerning the cost-effectiveness of OPT, CRT-P or CRT-D in treating persons with heart failure*

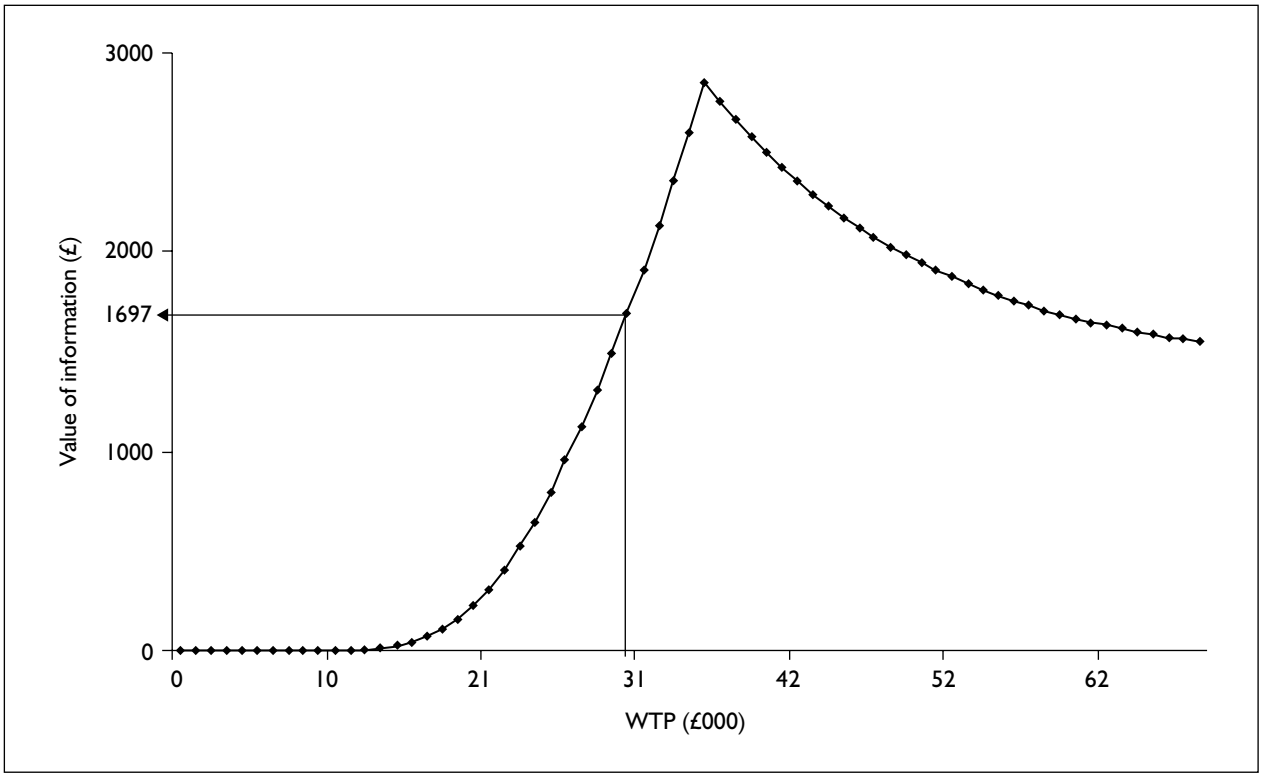

FIGURE 63 *Total EVPI at the person level (CRT-D versus CRT-P)*

generated. Plots of EVPI for the three-way comparison bear strong similarities to this plot, and therefore further information on the two-way comparison will directly influence the value of information in the three-way comparison.

At a WTP threshold of £30,000, the model predicts that the upper limit of value that could be obtained from acquiring perfect information on all input parameters would be around £1697 per patient based on the levels of uncertainty recorded for the initial model parameters (*Figure 63*).

Population-level EVPI for CRT-D versus CRT-P

Based on an assumed 6300 patients per year in England and Wales receiving CRT and a decision horizon of 7 years (approximately the mean lifetime of a device), the total EVPI at the population level is £67.6 million. The calculation was performed using a WTP threshold of £30,000 per QALY (*Figure 64*).

The value of information (£67.6 million) suggests further research would be beneficial.

Total EVPPI

The maximum decision uncertainty is generated when CRT-D is compared with CRT-P. Therefore, further information would have the greatest impact on this particular decision, so the EVPI value is very high.

Further investigation using EVPPI gave the results shown in *Figure 65*.

These results show that the maximum reduction in decision uncertainty is £50,533,659 for all HRs, £19,598,480 for SCD and £36,732,387 for death due to worsening HF. Therefore, further information on these parameters could have a significant impact on decision uncertainty.

Additional information on transition probabilities, costs, utilities and OPT survival curve parameters, transition probabilities, costs and utilities would have a negligible impact on decision uncertainty.

A summary of the model uncertainty is presented in *Table 73*.

Comparison of industry and PenTAG economic evaluations

Comparison of PenTAG and industry analyses

For simplicity, we compare the PenTAG analyses with the two main joint industry submissions only.

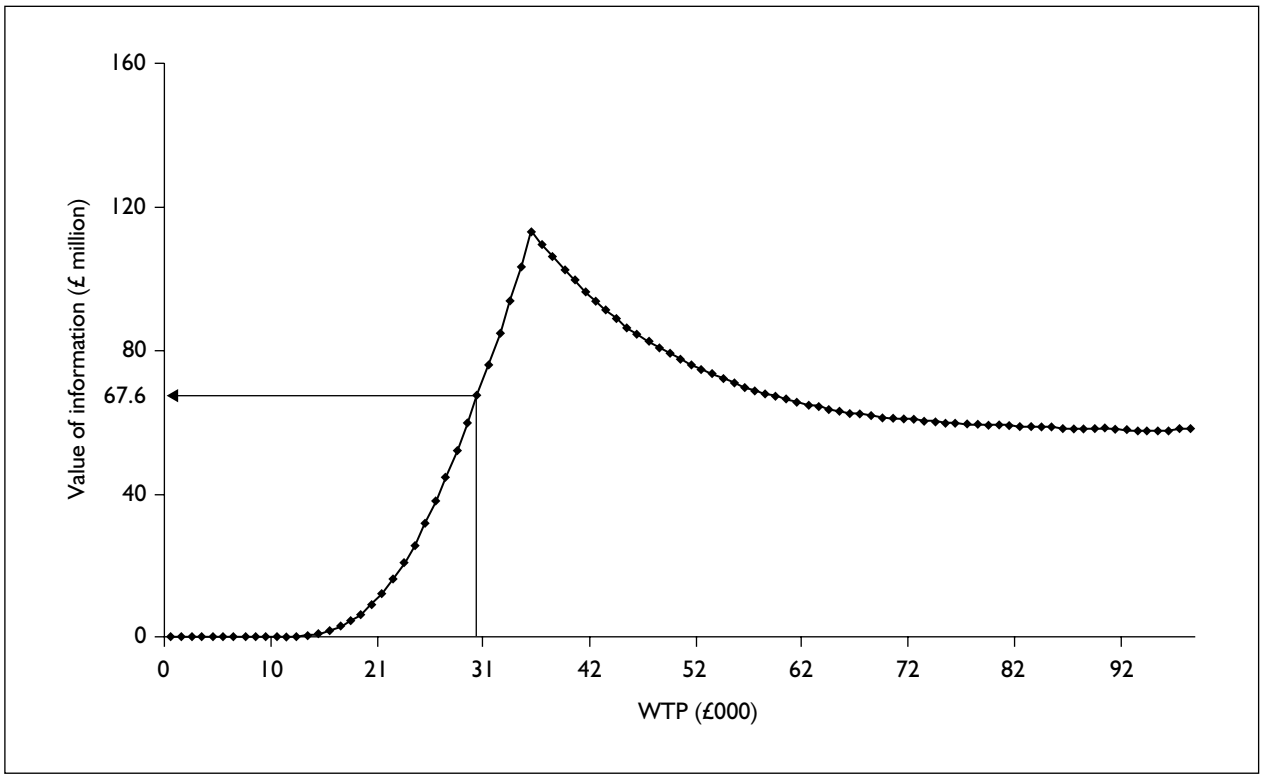

FIGURE 64 *Total EVPI at the population level (CRT-D versus CRT-P)*

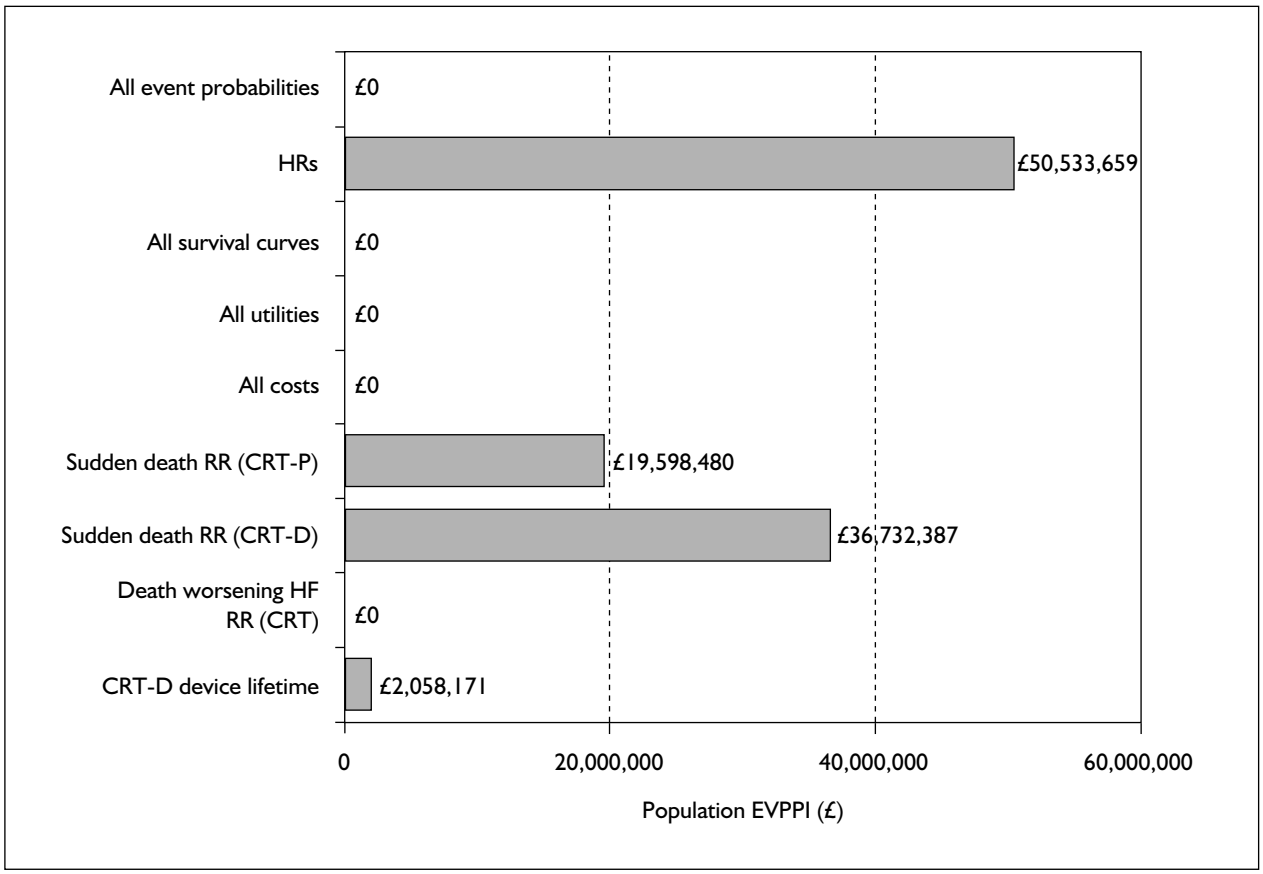

FIGURE 65 *EVPPI for CRT-D versus CRT-P*

TABLE 73 *Summary of model uncertainty*

	Source of variable	Level of uncertainty in the data	Impact of uncertainty on the model	Overall rating of importance
Transitions				
Device lifetime	Clinical trial Expert opinion Industry	Low to moderate	Low to moderate	Moderate
HF hospitalisation	Systematic review	Low	Moderate	Moderate
Surgical complication	Systematic review	Low	Low	Low
Arrhythmic event	Systematic review	Low	Moderate	Moderate
Survival	Systematic review	Low	Moderate to high	High
Utilities				
NYHA class	Systematic review	Low	Low	Low
Hospitalisation for HF	Systematic review	Low	Low	Low
Costs				
Implantation CRT-P	NHS PASA	Low	Low	Low
Implantation CRT-D	NHA PASA	Low	High	High
Device replacement	NSRC	Low	High	High
Treatment of infection	NSRC	Low	Low to moderate	Low to moderate

TABLE 74 *Base case incremental cost per QALY, by source of analysis*[a]

From comparator	To comparator	PenTAG lifetime analysis (£)	PenTAG 5-year analysis (£)	Joint industry (CARE-HF-based) (£)	Joint industry (COMPANION-based) (£)
OPT	CRT-P	16,735	24,256	15,645	2,818
OPT	CRT-D	23,650	37,443	Not produced	22,384
CRT-P	CRT-D	40,160	84,891	Not produced	Not produced

[a] These are the deterministic results from each analysis (i.e. based on the best, or base case, point estimate of each input parameter).

(In a previous section, Chapter 4, p. 40, we have appraised the CEA in the separate Guidant submission, but because it is essentially an abbreviated version of what was provided in the joint submission, with the same results for CRT-P versus OPT, we omit it from the comparisons below.) Also, in order to show the separate effect of the longer, until death, time horizon used by the PenTAG analysis, most of the comparisons discussed below are between the industry analyses and the PenTAG 5-year analysis.

Finally, although we compare the industry-submitted analyses of CRT-D versus OPT with the PenTAG estimates for the same comparison, this is done for completeness and to make the best use of the information provided in the industry submissions. The usefulness to decision-makers of making this cost-effectiveness comparison is highly questionable, given that the obvious comparator for CRT-D should be the next cheapest and best alternative health technology for this patient group, namely CRT-P.

Comparison of results

As shown in *Table 74*, the ICERs from the industry-submitted analyses (deterministic results) are all substantially lower than the equivalent estimates from the PenTAG 5-year analysis. The cost-effectiveness estimates for CRT-P from the COMPANION-based analysis are lower by over £20,000 per QALY and those from the CARE-HF-based analysis are nearly £10,000 lower. The differences between the mean results of each of the PSAs were similar.

These differences in the ICER estimates are due to the industry-submitted analyses having both lower estimated costs, and higher estimated QALY gains, of CRT compared with OPT (*Tables 75* and *76*). In the PenTAG 5-year analysis, the discounted incremental cost of CRT-P compared with OPT is

TABLE 75 *Base case total cost, by source of analysis*

Analysis	Discounted cost (£)			Incremental cost (£)	
	OPT	CRT-P	CRT-D	CRT-P vs OPT	CRT-D vs OPT
PenTAG analysis (30-year) (lifetime)	9,375	20,997	32,687	11,630	23,320
PenTAG analysis (5-year)	5,394	13,950	22,273	8,556	16,879
Joint industry (CARE-HF-based)	4,413	11,059	NR	6,646	NR
Difference vs PenTAG lifetime analysis	–4,962	–9,938	–	–4,984	–
Difference vs PenTAG 5-year analysis	–981	–2,891	–	–1,910	–
Joint industry (COMPANION-based)	11,546	13,028	24,832	1,482	13,286
Difference vs PenTAG lifetime analysis	2,171	–7,969	–7,855	–10,148	–10,034
Difference vs PenTAG 5-year analysis	6,152	–922	2,459	–7,074	–3,593

NR, not reported.

TABLE 76 *Base case QALYs, by source of analysis*

Analysis	Discounted QALYs			Incremental QALYs	
	OPT	CRT-P	CRT-D	CRT-P vs OPT	CRT-D vs OPT
PenTAG analysis (lifetime)	3.10	3.80	4.09	0.70	0.99
PenTAG analysis (5-year)	2.22	2.57	2.67	0.35	0.45
Joint industry (CARE-HF-based)	2.40	2.82	NR	0.42	NR
Difference vs PenTAG lifetime analysis	–0.7	–0.98	–	–0.28	–
Difference vs PenTAG 5-year analysis	0.18	0.25	–	0.07	–
Joint industry (COMPANION-based)	**2.14**[a]	**2.75**[a]	**2.85**[a]	0.526	0.594
Difference vs PenTAG lifetime analysis	–0.96	–1.05	–1.24	–0.174	–0.396
Difference vs PenTAG 5-year analysis	–0.08	0.18	0.18	0.176	0.144

NR, not reported.
[a] Figures in bold, not discounted.

£8556, whereas the two industry-submitted analyses estimate that CRT-P costs an additional £6646 or £1482 over 5 years. These industry-submitted incremental costs are 22% and 83% lower, respectively, than those estimated by the PenTAG model.

The estimated QALY gains due to CRT-P in each of the industry-submitted analyses (0.42 and 0.526) are 20% and 50% higher than those estimated by the PenTAG model (5-year analysis) (*Table 76*).These differences in estimated QALY gains are mainly a result of substantial differences in the estimated survival at 5 years.

The CARE-HF-based analysis estimates that an extra 11.7% of those initially receiving CRT-P would be surviving at 5 years than if they had stayed on OPT only. Similarly, the COMPANION-based analysis estimates that an extra 10.1% of those receiving CRT would be surviving at 5 years than if they had received OPT only. In comparison, the PenTAG analysis, in which mortality estimates are taken from a meta-analysis that includes both the CARE-HF and COMPANION trials, suggests a much lower improvement in 5-year survival, of only 8% (*Figure 66*).

Also, the COMPANION-based analysis shows a 16% improvement in the proportion surviving to 5 years with CRT-D (compared with OPT), whereas the PenTAG analysis suggests only a 12% improvement in 5-year survival.

In contrast to the survival data used by each analysis, there are only small differences in the QoL-related utility weights used in the various analyses (*Figure 67*). The utility estimates used in the COMPANION-based industry analysis reflect incremental differences in utility between CRT-P and OPT which are only 0.01 higher than those in

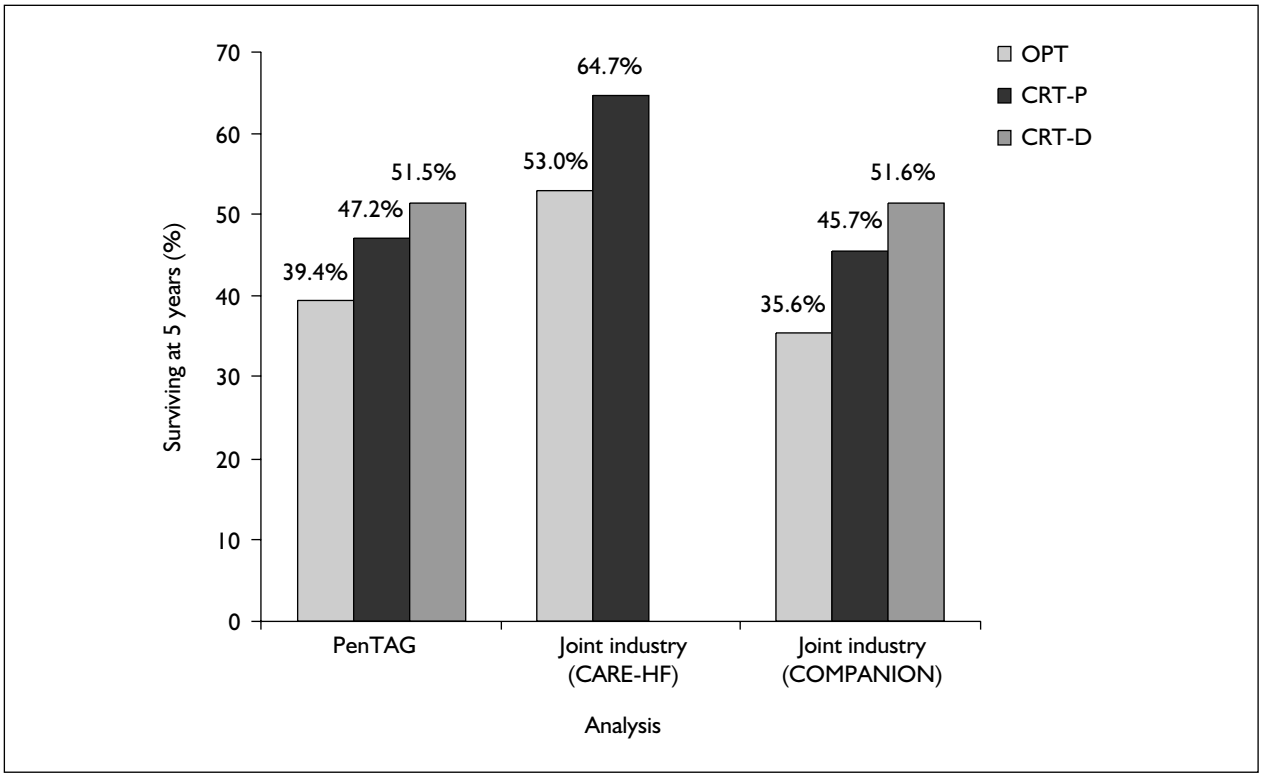

FIGURE 66 *Percentage surviving 5 years, by source of analysis. Sources: PenTAG, PenTAG analysis; Joint industry (CARE-HF), Leyva* et al.*, paper in press, Table 1; Joint industry (COMPANION), industry-submitted report from United BioSource Corporation, p. 7.*

the PenTAG analysis (which were derived directly from available CARE-HF data). Therefore, the higher incremental QALYs produced by both the industry-submitted analyses are either a result of incorporating survival data from single trials (which favour CRT more strongly than the PenTAG synthesis of mortality data from all relevant trials), or a result of how these trial-based mortality estimates were extrapolated to longer time horizons. Appendix 7 gives full tables of PenTAG's 5-year base case cost-effectiveness results and tables of undiscounted results over a lifetime time horizon.

Comparison of model inputs and structures

As much as possible, given the different model structures and different methods for simulating hospital costs, etc., *Table 77* shows the base case value of key model parameters for each analysis. It shows that whereas the PenTAG analysis used initial CRT implantation costs that were lower than in the other two analyses, either the unit cost and/or the event rates of subsequent hospitalisations and CRT-related complications must have been higher in the PenTAG analysis. For example, the COMPANION-based analysis did not include battery replacements (i.e. CRT unit replacement) in the base case analysis, and the rate of 'device revision' in the CARE-HF-based analysis was 160 after 5 years, out of 1000 originally attempted implants. Although neither of the industry-submitted analyses included the cost of OPT medications, this is unlikely to be a major cause of cost differences between them both and the PenTAG analysis.

Although the differences in model structure prevent some comparisons, a fuller presentation, in the industry submissions, of the 5-year event counts for specific types of CRT-related complications, and other types of hospital admissions, would have made it easier to analyse the source of the differences between the industry-submitted CEAs and the PenTAG analysis. Leyva and colleagues' unpublished paper goes some way towards providing this, with its table of 'predicted adverse outcomes and complications over 5 years'. Unfortunately, however, they do not describe the causes of and procedures involved in CRT 'revision' and CRT 're-implantation'. It is not clear, for example, whether and how the cost of lead replacement are included in the industry-submitted analyses.

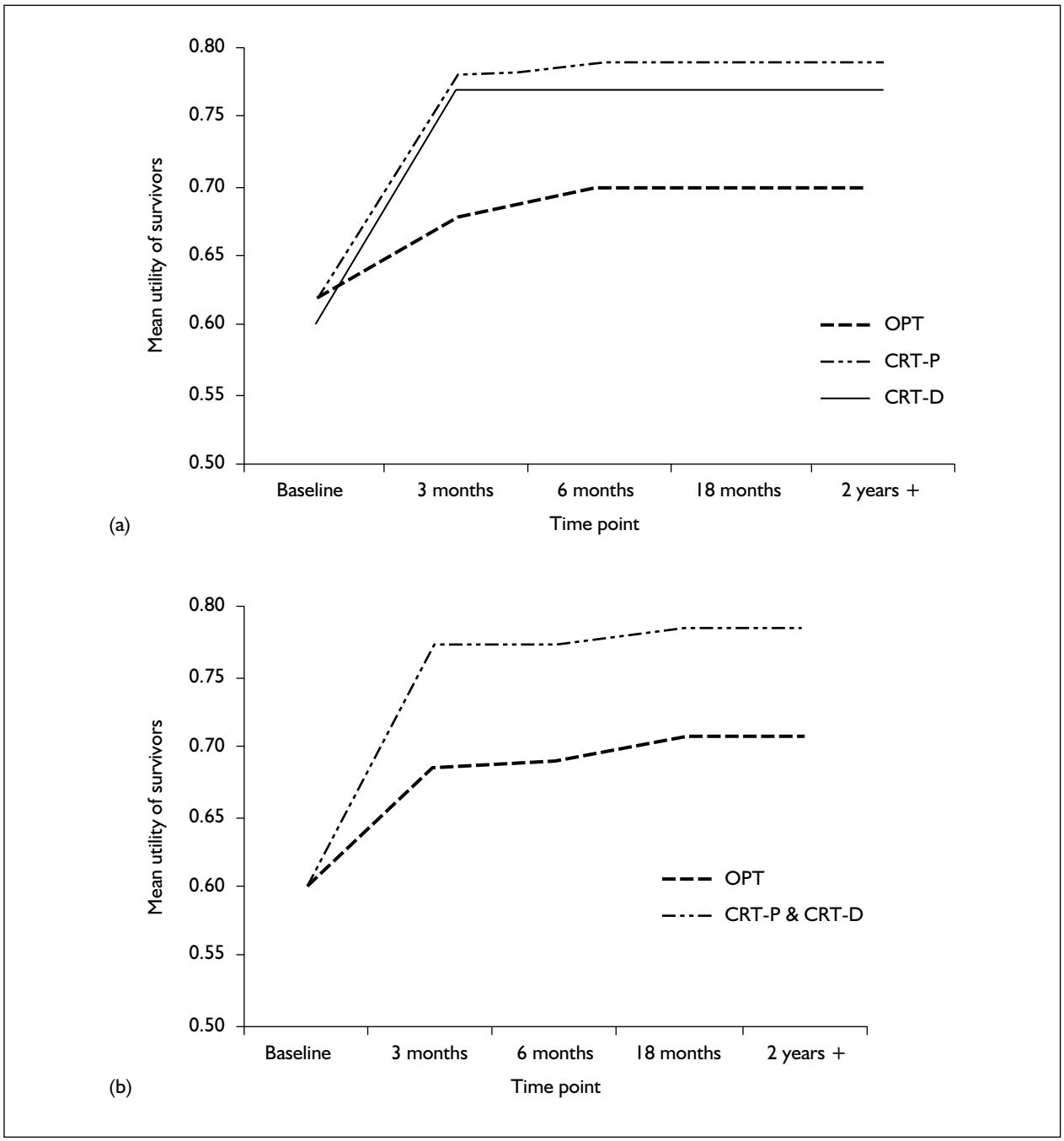

FIGURE 67 *Comparison of the utility weights used in each analysis. (a) Utility values in COMPANION-based analysis; (b) CARE-HF utility values, also in PenTAG analysis.*

TABLE 77 *Comparison of key model parameters*

Model characteristic or parameter	PenTAG analysis (lifetime time horizon)	Joint industry (CARE-HF-based)	Joint industry (COMPANION-based)
Model design	Decision tree with Markov model	Decision tree with discrete event simulation	Decision tree
Time horizon	Until death	5 years	5 years
Cost parameters			
CRT-P implantation, with device cost	£5,074	£8,106[a]	£7,432
CRT-D implantation, with device cost	£17,266	NA	£18,711
Unsuccessful implant	Same cost as successful	£4,266	–
Treating lead infection (with CRT-P)	£9,384	Not stated	In all-cause hospital admission
Treating lead infection (with CRT-D)	£20,625	Not stated	In all-cause hospital admission
Battery failure/unit replacement	£5,074	Revision: £2,566 Reimplantation: £8,106[a]	Not included in base case
ICD implantation, with device	£11,596		In all-cause hospital admission
OPT medication costs	Yes – from £5 to £15 per person per 4 weeks	Not included	Not included
Effectiveness parameters			
All-cause mortality (CRT-P)	HR = 0.71	NYHA-specific rate, per person per day: I = 0.00065[b] II = 0.00186[b] III = 0.000277[b] IV = 0.001208[b]	HR = 0.76
All-cause mortality (CRT-D)	HR = 0.71	NA	HR = 0.64
All-cause hospitalisation (CRT-P)	Rate ratio CRT vs OPT, for HF: 0.65 HR CRT-P and CRT-D vs OPT, for SCD: 0.75 and 0.44	NYHA-specific rate, per person per day: I = 0.000724[b] II = 0.001158[b] III = 0.002165[b] IV = 0.004964[b]	Not reported
Unsuccessful implants	9.38%	9.4%	Not reported

NA, not applicable.

[a] CRT implantation costs in the Leyva *et al*. (unpublished) analysis included procedure, hospital stay, device and follow-up costs in the first year.

[b] Hazard rates for mortality and hospitalisations reported in Table 1 of Leyva *et al*. (unpublished paper). Note that there is probably a typographic error in this table as the mortality data imply that the mortality rates increase from NYHA class III to I to IV to II.

Summary of cost-effectiveness

1. PenTAG designed a Markov model to assess the cost-utility of CRT-P versus OPT, CRT-D versus OPT and CRT-P versus CRT-D.
2. A mixed age, mixed sex cohort of 1000 people was modelled until death.
3. The base case showed that:
   (a) CRT-P conferred an additional 0.70 QALYs for an additional £11,630 per person, giving an ICER of £16,735/QALY.
   (b) CRT-P versus CRT-D conferred an additional 0.29 QALYs for an additional £11,689 per person, giving an ICER of £40,160/QALY.
   (c) CRT-D conferred an additional 0.99 QALYs for an additional £23,320 per person, giving an ICER of £22,650/QALY.
4. One-way sensitivity analyses showed that the model was particularly sensitive to model time horizon, device lifetime, discount rate applied to health benefit, probability of an arrhythmic event, risk of SCD and the risk of death from worsening HF.
5. PSA based on 1000 simulated trials showed that at £30,000/QALY:
   (a) CRT-P versus OPT: CRT-P was likely to be cost-effective in 91.3% of simulations and CRT-P was negatively dominated in 0.4% of simulations.
   (b) 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.
   (c) CRT-D versus OPT: CRT-D was likely to be cost-effective in 73.2% of simulations and CRT-D was negatively dominated in 0.3% of simulations.
6. When OPT was considered as a competing technology to CRT-P and CRT-D, there was a 68% probability that CRT-P provided the highest expected net benefit at £30,000/QALY. The WTP threshold would need to be £40,160 before CRT-D provided the highest expected net benefit.

Chapter 6

Assessment of factors relevant to the NHS and other parties

Implications for service provision

The future development of CRT provision within the NHS is dependent upon both access to suitably trained cardiologists and associated clinical staff and the adequate provision of implantation centres and associated diagnostic infrastructure.

Our clinical advisers have suggested that: (1) the current availability of cardiologists with the necessary skills to undertake CRT surgery is one to two per regional centre, and this will increase to an additional one per district general hospital as further cardiologists are trained, and (2) the learning curve for CRT implantation is steep and training should be undertaken by senior and experienced implanters of conventional pacemakers and ICDs. Furthermore, resources will be needed for associated clinical staff, technicians and the related diagnostic infrastructure including properly equipped cardiac catheter laboratories.

Implications for patients and carers

The expected improvement in health gain for people provided with CRT should have concomitant effects on their family and carers, as the impact of HF on their lives is reduced.

Chapter 7
Discussion

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

Statement of principal findings

Clinical effectiveness

Five RCTs of moderate to good quality were included in the systematic review. Trials recruited a total of 3434 people who had evidence of LVSD (ejection fraction ≤35%) and cardiac dyssynchrony (QRS interval >120 ms) despite OPT. In all but one trial (CONTAK-CD), these people were in NYHA classes III and IV. Four trials provided data on CRT-P compared with OPT alone, two trials provided data on CRT-D compared with OPT and one trial provided a direct comparison of CRT-D and CRT-P.

Meta-analysis showed that people implanted with the CRT-P devices experienced reduced risk of all-cause mortality (HR 0.68, 95% CI 0.54 to 0.88, $p = 0.001$), death from heart failure (HR 0.62, 95% CI 0.46 to 0.83, $p < 0.0001$) and hospitalisation for HF (HR 0.48, 95% CI 0.37 to 0.61, $p < 0.0001$) after up to 3 years of follow-up, compared with those people on OPT. However, there was no significant reduction in SCD with CRT-P (HR 0.75, 95% CI 0.45 to 1.18, $p = 0.198$).

For those implanted with CRT-D devices, the risk was reduced for all-cause mortality (HR 0.65, 95% CI 0.49 to 0.85, $p < 0.0001$) and SCD (HR 0.44, 95% CI 0.23 to 0.86, $p < 0.02$), compared with OPT after up to 16 months of follow-up. No significant reduction was seen in death due to HF with CRT-D (HR 0.73, 95% CI 0.47 to 1.11, $p = 0.143$).

Compared with OPT, both devices significantly improved exercise capacity, health-related QoL and NYHA class at 3–6 months. There was little evidence of heterogeneity across trials.

Direct comparison between CRT-P and CRT-D showed no significant difference in outcomes with the exception of SCDs, which were significantly higher with CRT-P (RR 2.02, 95% CI 0.49 to 8.78, $p = 0.345$).

No statistically significant difference in CRT effects was seen across predefined subgroups (i.e. age, NYHA class, ischaemic versus non-ischaemic aetiology, QRS duration or ejection fraction). This negative result probably reflects a combination of lack of power in trials.

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 in the short term. Over 90% of implants were successful, the main problem being locating and securing the left ventricular lead. There was no evidence to suggest a difference in the risk of complications between the two devices.

CRT had positive effects on QoL. An eight-point change in the MLWHF questionnaire is associated with a clinically important difference in health-related QoL.[114] The magnitude of effect seen here (pooled mean difference in MLWHF: CRT-P versus OPT, –9.9, 95% CI –12 to –7.6; CRT-D versus OPT, –13.3, 95% CI –16.6 to –10.1), indicates that CRT provides important QoL benefits.

Although there is a placebo effect to pacemaker implantation,[51] objective data show that the benefits of CRT are real and sustained (CARE-HF) and that the placebo effect appears to wane over time (MIRACLE).

These findings are in accord with previous systematic reviews and meta-analyses, albeit they had somewhat different inclusion criteria.

Cost-effectiveness

Summary of previously published economic evaluations

There were no published economic evaluations of CRT-P or CRT-D in UK populations of HF patients or from an NHS perspective. The cost-effectiveness of CRT appears to depend on the time horizon of the analysis. No evaluations had a time horizon of longer than 5 years, therefore excluding the costs of periodic CRT unit (battery) replacement.

Summary of industry-submitted economic evaluations

The analyses submitted by industry to NICE were generally well described and conducted to accepted methodological standards. However, they used only a 5-year time horizon, and may have used optimistic rates of CRT-related complications. One was based on clinical effectiveness data from a number of European countries (CARE-HF trial) and the other was based on US trial data (COMPANION trial). Their estimated ICERs were £15,645 and £2,818 per QALY gained for CRT-P versus OPT and £22,384 per QALY gained for CRT-D versus OPT.

Summary of PenTAG's model-based cost–utility analysis

The PenTAG model used a lifetime time horizon. Parameters were largely populated from this assessment's systematic review and other high-quality sources. The results estimate that CRT-P confers 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 confers 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 QALY gains and failing to include the costs incurred from repeated replacement of devices due to modelling only 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 SCD and the risk of death from worsening HF.

PSA based on 1000 simulated trials showed that, at a 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 QoL you receive), in 0.4% of simulations.
- **CRT-D versus CRT-P:** 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 RR of SCD 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 with OPT, 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 £40,000 or above before CRT-D would provide the highest expected net benefit.

Value of information analyses

An important reason for characterising parameter uncertainty is to establish the value of additional information on any decision made. The EVPPI for the comparisons was as follows:

- **CRT-P versus OPT:** These results indicated that the maximum reduction in decision uncertainty is £2,354,829 for all HRs and £1,144,427 for all survival curves. Therefore, further research on these parameters could have a significant impact on decision uncertainty. Further information on other parameters would have a negligible impact.
- **CRT-D versus CRT-P:** These results showed that the maximum reduction in decision uncertainty is £50,533,659 for all HRs, £19,598,480 for SCD and £36,732,387 for death due to worsening HF. Therefore, further research on these parameters could have a significant impact on decision uncertainty. Additional information on transition probabilities, costs, utilities and OPT survival curve parameters, transition probabilities, costs and utilities would have a negligible impact on decision uncertainty.

Strengths and limitations of the assessment

Strengths

The strengths of this assessment are that it is comprehensive, systematic, up-to-date and conducted by an independent research team.

The main strengths of the economic model are that it produces results for a mixed age starting cohort rather than for a single age starting cohort, as is usually the case with a Markov model. Using a mixed age cohort allows subgroup analyses by age of CRT recipients, and produces results that are more realistic for policy making. The model is also populated by effectiveness estimates largely sourced through the systematic review and meta-analysis.

The model allows for people to have a change of device following battery failure which more closely mirrors clinical practice.

The model also allows people to have failed operations and revert back to OPT over the course of their remaining lives, again reflecting real-world clinical practice.

Limitations of the clinical systematic review

There are a number of limitations of the clinical systematic review that relate to the included studies and the scope of the report.

Generalisability

There is some concern about the generalisability that arises from the scope and the nature of the individual trials. With the exception of CARE-HF and COMPANION, these were trials of efficacy rather than effectiveness. The populations of the efficacy trials may not be representative as they only reported outcomes of individuals who had survived their operation and were doing well after a postimplant recovery period (rather than individuals with HF who were recruited and randomised pre-implantation). Therefore, the outcomes of the efficacy studies may overestimate the benefits and underestimate the adverse effects of CRT. However, by combining these data with the large CARE-HF and COMPANION trials in the meta-analysis, it is expected that these distortions will have been mitigated.

Atrial fibrillation

None of the trials in this systematic review included people with AF. Our informal literature searches identified no consistent evidence[100–105] to support the use of CRT in people with permanent AF.

Adequacy of time horizon of trials

Three of the trials (CONTAK-CD, MIRACLE and MUSTIC-SR) followed participants for 6 months. COMPANION had a mean follow-up time of 15 months and CARE-HF followed people for a mean of 36 months. This report is interested in outcomes over a lifetime. Although the dangers of extrapolation are acknowledged, having data for 36 months might be considered adequate for a 65-year-old with HF on OPT where the mean life expectancy is 5.7 years (PenTAG model). Nevertheless, longer-term data are needed to assess fully the safety of CRT devices, particularly given the recent experiences with stand-alone ICD devices.[138–140]

Limitations of the PenTAG economic model

There is some structural uncertainty in the PenTAG model. This refers to the choice both of Markov methodology instead of a discrete event approach, and the Markov states and allowable transitions between them.

The model aggregates all perioperative complications into one state and is limited to only the main perioperative adverse events. This is a potential limitation of the model, but given the rarity of the events ignored (e.g. hypotension or heart block), the effect is not expected to be significant.

We have assumed that postoperative complications (with the exception of lead displacement) have a constant probability. This is a potential limitation as events may be more likely to occur soon after device implantation rather than maintain the same level of probability throughout a lifetime. Data are not available to confirm this assumption.

Trials did not disaggregate their report of the outcomes of responders and non-responders. We were therefore unable to model explicitly the separate effect of non-responders or failures.

The structure of the model is not explicitly predicated on patients' NYHA classes, so event rates and mortality are not stratified into four separate classes. Given that classifying a person's state of health by NYHA class is a widely recognised and accepted method in the cardiology community, this may make the model less transparent to the desired readership and may therefore be seen as a weakness. However, it is important to note that NYHA class is incorporated into the model, with both drug costs and QoL (utility weights) being driven by specified mixes of patients of different NYHA class.

The modelled population is based as far as possible on the systematic review of published RCTs and also on any observational studies relevant to the underlying decision problem. Given that HF is a progressive syndrome, and that despite its seriousness people can be expected to live longer than the follow-up period of included trials, extrapolation of trial data was required for some important model parameters. The assumption that any short-term mortality reductions and QoL improvements observed in trials continue until death is a strong one, and the effect on model outputs is difficult to assess.

Similarly, published trial results represent aggregates over all participants, and can therefore be thought of as aggregates of the effects in all age categories. The PenTAG model has assumed that event probabilities (e.g. serious arrhythmic events and lead displacements) are independent of age.

Remaining uncertainties in the evidence base

CRT-D versus CRT-P devices

There is limited head-to-head evidence for the two devices. Consequently, the relative clinical effectiveness and cost-effectiveness of the devices is particularly uncertain. The necessary use of indirect comparison to establish the cost-effectiveness of CRT-P compared with CRT-D means that the results should be treated with caution. The question therefore remains as to which group of HF people should receive a CRT-D device. The CONTAK-CD and MIRACLE ICD[141] trials (comparing CRT-D with ICD) give some insight into this issue as they both included people with conventional ICD indications (in addition to CRT indications); these trials reported little benefit from adding CRT to ICD.

Long-term benefits and adverse events

Evidence from the CARE-HF extension study (36 months) indicates that the benefits of CRT are sustained in people with both ischaemic and non-ischaemic heart failure.[142] However, long-term effectiveness and safety remain unclear.

NYHA classes I and II

As people within these classes of functional ability were largely excluded from the included trials, we have been unable to comment on the possible benefits that they might receive from CRT.

Correlation of inputs

There are several parameters in the model which, in reality, are likely to be correlated (e.g. the probability of an arrhythmic event, the probability of sudden death and CRT-D device lifetime). It would be possible to build in interactions between such parameters into the model if there was information about the correlation between the parameters. We have no such information and so as a result have modelled them as independent events. The effect of this is to introduce uncertainty into the model.[143] However, there is no impact on the base case ICERs as these are not generated probabilistically. Uncertainty also remains around the utility weights for the QoL impact of CRT and the lifetime of CRT devices.

Implications for service provision

It is likely that more resources will be needed to train cardiologists and associated staff to cope with increased demand for CRT in the event of more widespread adoption. Provision for the related infrastructure is also likely to require further resources. Further work is required to specify implications for local services.

Suggested further research priorities

Future research priorities need to take account of the substantial numbers of ongoing trials for CRT devices (see Appendix 8).

Identification of non-responders

A number of studies have identified characteristics of non-response.[96] However, we have been unable to find a systematic review of these studies which would determine the methods that most accurately identify those people with HF who will not benefit from this therapy. Further primary studies are also needed in this area, such as trials that recruit and include patients based on evidence of dyssynchrony using both ECG and ECHO technologies. This may be forthcoming from the results of the PROSPECT trial which is using left ventricular remodelling as a primary end-point.[144]

Atrial fibrillation

A proportion of people with HF also have AF. Therefore, it is important for trials to be conducted to establish whether CRT is effective in this group.

NYHA classes I and II

With the exception of CONTAK-CD, the trials in this systematic review excluded people with asymptomatic or mild HF (i.e. NYHA classes I or II). There is some suggestion that such patients may benefit from CRT.[114] Well-conducted trials powered to detect difference in mortality and HF hospitalisation are needed. The ongoing MADIT-CRT and REVERSE trials will evaluate the role of ICDs with and without CRT in large cohorts of people with NYHA class I and II HF.

Long-term safety data

Results indicate that CRT-P and CRT-D are relatively safe in the short term. However, this was also true of ICD trials, whereas recent 'real-world' experience found that a number of ICDs failed.[138–140] A recent meta-analysis of safety outcomes in ICD-implanted people reported there

to be little or no long-term real observational data on CRTs.[145] We know of no current system for the collection of long-term outcome data (benefits and risks) on CRT implants in the UK as part of a nationally coordinated registry such as the British Pacing and Electrophysiology Group registry for conventional pacemakers.

Appropriate use of CRT-D devices

Only the COMPANION study provided data that allowed a direct comparison between CRT-P and CRT-D. This trial randomised people to receive CRT-P or CRT-D after excluding people with conventional ICD indications Further trials are needed to address which specific group of people with HF should receive a CRT-D device (see Appendix 8).

Based on the EVPPI 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 those receiving OPT.

Chapter 8
Conclusions

In people with NYHA classes III and IV HF and sinus rhythm with QRS >120 ms, CRT-P and CRT-D devices reduce mortality and hospitalisations due to HF and improve health-related QoL. Additionally, CRT-D devices reduce risk of SCD. 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 alone.

When measured on a lifetime time horizon and compared with OPT, CRT-P is estimated to be cost-effective at a WTP threshold of either £20,000 or £30,000 per QALY. CRT-P is likely to be considered cost-effective at a WTP threshold of £20,000 per QALY compared with OPT.

However, the comparison of CRT-D with CRT-P showed that there was unlikely to be a net monetary benefit in using CRT-D at a WTP threshold of less than £40,000 per QALY.

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Contribution of authors

Rob Anderson (Health Economist) obtained costs for the model, contributed to writing the report (assessment of cost-effectiveness chapter), led the critique of the economic evaluations from the manufacturers and contributed to the design and development of the model and the editing of the report. Mary Fox (Research Fellow) provided overall project management, wrote the protocol, assessed abstracts for inclusion and exclusion, extracted data, led the writing and editing of the report, contributed to the design of the model and identified model input data. John Dean (Consultant Cardiologist) contributed to the development of the protocol, contributed to the editing of the report, provided clinical input into the model design and advised on clinical matters. Stuart Mealing (Research Assistant) designed, developed and executed the economic model and contributed to the writing of the report (assessment of cost-effectiveness chapter). Alison Price (Information Scientist) undertook literature searches for the project and commented on drafts of the protocol and the TAR. Ken Stein (Senior Lecturer in Public Health) contributed to the design of the assessment, the design and development of the model and the preparation and editing of the report. Rod Taylor (Reader in Health Services Research) assessed abstracts for inclusion and exclusion, extracted data, contributed to the design of the model, undertook the meta-analysis, contributed to the economic evaluation from the manufacturers and contributed to the writing and editing of the report.

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Appendix 1

Literature search strategies

Clinical searches

A wide range of databases and other information resources were searched to locate details of both published and unpublished studies and other information on the clinical effectiveness and cost-effectiveness of CRT (BVP) for HF.

All resources were searched from their inception to the most recent date available. There was no restriction on study by language or publication date. The bibliographies of retrieved references were checked for additional publications. The results of the searches were imported into Reference Manager 11 bibliographic management software and reduplicated. All initial searches were carried out in January 2006 and the update searches were re-run in June 2006.

The following databases were searched: MEDLINE (Ovid), EMBASE (Ovid), Ovid MEDLINE® In-Process and Other Non-Indexed Citations, ISI Science Citation Index, Cochrane Database of Systematic Reviews, CENTRAL, NHS EED, DARE, HTA (NHS-CRD), EconLit, Biosis Previews, ISI Proceedings, Current Controlled Trials, National Research Register and Clinical Trials.gov.

Relevant Internet sites were searched for information, including the following regulatory sites: Medical Health and Regulatory Agency (MHRA), US Food and Drugs Administration (FDA) and the European Regulatory Agency – Medical Device Safety Service (MDSS).

Full search strategies are listed below.

Databases and years searched	Date searched and search files
Cochrane Library – CDSR – 2005 Issue 4 Searched 16 January 2006	**#1** CRT or cardiac resynchron* therap* **in** All Fields **in** all products **278** **#2** resynchron* therap* **in** All Fields **in** all products **49** **#3** BVP **in** All Fields **in** all products **8** **#4** biventricular NEAR pac* **in** All Fields **in** all products **48** **#5** biventricular NEAR stimulat* **in** All Fields **in** all products **6** **#6** (cardiac or heart or coronary) NEAR resynch* **in** All Fields **in** all products **42** **#7** atriobiventricular NEAR pac* **in** All Fields **in** all products **2** **#8** CRT-P or CRT-D **in** All Fields **in** all products **10** **#9** (#1 **OR** #2 **OR** #3 **OR** #4 **OR** #5 **OR** #6 **OR** #7 **OR** #8) **317** **#10 MeSH descriptor** Heart Failure, Congestive **explode all trees in** MeSH products **3088** **#11** (heart NEAR failure) **in** All Fields **in** all products **6433** **#12** (chf or chronic heart failur*) **in** All Fields **in** all products **2826** **#13 MeSH descriptor** Cardiac Pacing, Artificial **explode all trees in** MeSH products **531** **#14 MeSH descriptor** Pacemaker, Artificial **explode all trees in** MeSH products **353** **#15** (#10 **OR** #11 **OR** #12 **OR** #13 **OR** #14) **7587** **#16** (#9 **AND** #15) **77**
Cochrane Library – CENTRAL – 2005 Issue 4	As above
Ovid MEDLINE(R) 1966 to December Week 4 2005 Searched 11 January 2006	1 (CRT or "cardiac resynchron$ therap$").ti,ab. (2173) 2 resynchron$ therap$.ti,ab. (455) 3 BVP.ti,ab. (110) 4 (biventricular adj10 pac$).mp. (566) 5 (biventricular adj10 stimulat$).mp. (84) 6 ((cardiac or heart) adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (532)

continued

Databases and years searched	Date searched and search files
	7 (coronary adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (20) 8 (atriobiventricular adj10 pac$).mp. (7) 9 CRT-P.mp. (30) 10 CRT-D.mp. (4) 11 (insync or contak or "epic hf" or ovatio or situs or "newliving" or alto).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3360) 12 or/1-11 (6148) 13 exp Cardiac Pacing, Artificial/ (13395) 14 exp Pacemaker, Artificial/ (17098) 15 exp Cardiomyopathy, Dilated/ (8550) 16 Heart-Assist Devices/ (4254) 17 exp Heart Conduction System/ (29066) 18 exp Arrhythmia/ (111066) 19 exp Ventricular Remodeling/ (2064) 20 Bundle-Branch Block/ (5690) 21 exp Heart Failure, Congestive/ (54150) 22 exp Ventricular Dysfunction, Left/ (8340) 23 (heart adj3 failure).mp. (71019) 24 (chf or chronic heart failur$).ti,ab. (9352) 25 chronic cardiac failure$.ti,ab. (311) 26 ((cardiac or ventricular or intraventricular) adj5 asynchron$).ti,ab. (290) 27 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).ti,ab. (113) 28 or/13-27 (209810) 29 12 and 28 (1090) 30 limit 29 to humans (1052) 31 randomized controlled trial.pt. (209265) 32 controlled clinical trial.pt. (69908) 33 randomized controlled trials/ (40111) 34 random allocation/ (54094) 35 double-blind method/ (84019) 36 single-blind method/ (9457) 37 exp evaluation studies/ (537716) 38 exp clinical trials/ (171619) 39 clinical trial.pt. (419502) 40 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (893587) 41 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw. (81222) 42 exp placebos/ (24252) 43 placebo$.tw. (92027) 44 random$.tw. (323773) 45 41 or 42 or 43 or 44 (391154) 46 40 or 45 (1040233) 47 46 and 30 (278) 48 meta-analysis/ (6326) 49 metaanalys$.ti,ab,pt. (499) 50 meta analys$.ti,ab,pt. (18339) 51 (systematic adj2 (review$ or overview$)).ti,ab. (8486) 52 or/48-51 (27287) 53 (comment or letter or editorial).pt. (761527) 54 52 not 53 (25196) 55 54 and 30 (8) 56 47 not 55 (271) 57 limit 56 to english language (232) 58 limit 55 to english language (8) 59 (55 or 56) not (57 or 58) (39)

continued

Databases and years searched	Date searched and search files
EMBASE 1980 to 2006 Week 1 Searched 13 January 2006	1 (CRT or "cardiac resynchron$ therap$").ti,ab. (2039) 2 resynchron$ therap$.ti,ab. (515) 3 BVP.ti,ab. (99) 4 cardiac resynchronization therapy/ (480) 5 (biventricular adj10 pac$).mp. (601) 6 (biventricular adj10 stimulat$).mp. (113) 7 ((cardiac or heart) adj10 resynch$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (852) 8 (coronary adj10 resynch$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (45) 9 (atriobiventricular adj10 pac$).mp. (9) 10 CRT-P.mp. (32) 11 CRT-D.mp. (9) 12 (insync or contak or "epic hf" or ovatio or situs or "newliving" or alto).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2229) 13 or/1-12 (5076) 14 exp Cardiac Pacing, Artificial/ (9969) 15 exp Pacemaker, Artificial/ (7728) 16 exp Cardiomyopathy, Dilated/ (5317) 17 Heart-Assist Devices/ (1657) 18 exp Heart Conduction System/ (8870) 19 exp Arrhythmia/ (118142) 20 exp Ventricular Remodeling/ (3113) 21 Bundle-Branch Block/ (752) 22 exp Heart Failure/ (85224) 23 exp Heart Failure, Congestive/ (20888) 24 exp Ventricular Dysfunction, Left/ (10453) 25 (heart adj3 failure).mp. (77282) 26 (chf or chronic heart failur$).ti,ab. (9496) 27 chronic cardiac failure$.ti,ab. (250) 28 ((cardiac or ventricular or intraventricular) adj5 asynchron$).ti,ab. (335) 29 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).ti,ab. (137) 30 or/14-29 (217519) 31 13 and 30 (1334) 32 limit 31 to humans (1264) 33 meta-analysis/ (24055) 34 metaanalys$.ti,ab,pt. (784) 35 meta analys$.ti,ab,pt. (12313) 36 (systematic adj2 (review$ or overview$)).ti,ab. (8095) 37 or/33-36 (34542) 38 (comment or letter or editorial).pt. (452160) 39 37 not 38 (32162) 40 32 and 39 (37) 41 limit 40 to english language (36) 42 random$.mp. or placebo$.ti,ab,sh. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (392244) 43 ((double$ or single$ or triple$ or treble$) and (blind$ or mask$)).ti,ab,sh. (85227) 44 (clinical trial or controlled clinical trial or major clinical study or controlled study).ti,ab,sh. (2886666) 45 42 or 43 or 44 (3006424) 46 45 and 32 (644) 47 46 not 40 (608) 48 limit 47 to english language (527) 49 from 41 keep 1-36 (36) 50 from 48 keep 1-527 (527)

continued

Databases and years searched	Date searched and search files
PreMEDLINE – Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 9 January 2006 Searched 11 January 2006	1 (CRT or "cardiac resynchron$ therap$").ti,ab. (195) 2 resynchron$ therap$.ti,ab. (112) 3 BVP.ti,ab. (5) 4 (biventricular adj10 pac$).mp. (58) 5 (biventricular adj10 stimulat$).mp. (7) 6 ((cardiac or heart) adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word] (129) 7 (coronary adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word] (8) 8 (atriobiventricular adj10 pac$).mp. (1) 9 CRT-P.mp. (4) 10 CRT-D.mp. (9) 11 (insync or contak or "epic hf" or ovatio or situs or "newliving" or alto).mp. [mp=title, original title, abstract, name of substance word] (77) 12 or/1-11 (315) 13 (heart adj3 failure).mp. (2002) 14 (chf or chronic heart failur$).ti,ab. (466) 15 chronic cardiac failure$.ti,ab. (3) 16 ((cardiac or ventricular or intraventricular) adj5 asynchron$).ti,ab. (13) 17 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).ti,ab. (34) 18 or/13-17 (2050) 19 12 and 18 (122) 20 (random$ or placebo$).mp. [mp=title, original title, abstract, name of substance word] (15425) 21 19 and 20 (16)
Science Citation Index 1970–2006 Searched 16 January 2006	TS=(CRT or cardiac resynchron* therap*) TS=(resynchron* therap*) TS=(BVP) TS=(biventricular SAME pac*) TS=(biventricular SAME stimulat*) TS=((cardiac or heart or coronary) SAME resynch*) TS=(atriobiventricular SAME pac*) TS=(CRT-P or CRT-D) #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 TS=((chf or chronic heart failur*)) TS=(heart SAME failur*) #11 OR #10 #12 AND #9 TS=(random* or placebo*) TS=(clinical SAME trial*) TS=(((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))) #16 OR #15 OR #14 #17 AND #13 TS=(meta analysis or metaanalysis) TS=((systematic SAME (review* or overview*)) #20 OR #19 #21 AND #13
Web of Science Proceedings Database STP; 2003–2006	26 #14 AND #9 304 #13 AND #6 *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006* 5,943 #12 OR #11 *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006* 5,800 TS=((heart SAME failur*)) *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*

continued

Databases and years searched	Date searched and search files	
	1,097	TS=(chf or chronic heart failur*) *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	69	#9 AND #6 *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	35,230	#8 OR #7 OR #4 *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	5,722	TS=(clinical SAME trial*) *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	31,687	TS=((random* or placebo*)) *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	1,071	#5 OR #3 OR #2 OR #1 *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	854	TS=((CRT OR cardiac resynchron* therap*)) *DocType=All document types; Language=All languages; Database=STP; Timespan=2003-2006*
	13,270	TS=(rct* or randomi*) *DocType=All document types; Language=English; Database=STP; Timespan=2003-2006*
	396	TS=(cardiac SAME resynchron* SAME therap*) *DocType=All document types; Language=English; Database=STP; Timespan=2003-2006*
	200	TS=(biventricular SAME pacing) *DocType=All document types; Language=English; Database=STP; Timespan=2003-2006*
	458	TS=(cardiac SAME resynchron*)
BIOSIS PREVIEWS 2003–2005 Meeting	((al: (rct)) or al: (randomi*) and dt= "Meeting" and yr: 2003-2005 and la= "English") and (al: (biventricular pacing) or al: (cardiac resynchron*) and al: (heart failure) and dt= "Meeting" and yr: 2003-2005 and la= "English")	
DARE	CRT or cardiac resynchron* therap* and heart failure* Biventricular pac* heart failure* Heart resynchron* and heart failure*	
NHS EED (on CRD databases)	CRT or cardiac resynchron* therap* and heart failure* Biventricular pac* heart failure* Cardiac or Heart resynchron* and heart failure*	
HTA database (on CRD databases)	CRT or cardiac resynchron* therap* and heart failure* Biventricular pac* heart failure* Heart resynchron* and heart failure*	
NRR (National Research Register)	Biventricular pac* or cardiac resynchron*	
Current Controlled Trials including MRC Trials dB http://controlled-trials.com/	"biventricular pac%" OR "cardiac resynchronization!"	
Clinical Trials.gov http://clinicaltrials.gov/	Biventricular pacing OR cardiac resynchronization	

Economics searches

Databases and years searched	Date searched and search files
Ovid MEDLINE(R) 1966 to December Week 4 2005 Searched 11 January 2006	1 (CRT or "cardiac resynchron$ therap$").ti,ab. (2173) 2 resynchron$ therap$.ti,ab. (455) 3 BVP.ti,ab. (110) 4 (biventricular adj10 pac$).mp. (566) 5 (biventricular adj10 stimulat$).mp. (84) 6 ((cardiac or heart) adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (532) 7 (coronary adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (20) 8 (atriobiventricular adj10 pac$).mp. (7) 9 CRT-P.mp. (30) 10 CRT-D.mp. (4) 11 (insync or contak or "epic hf" or ovatio or situs or "newliving" or alto).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3360) 12 or/1-11 (6148) 13 exp Cardiac Pacing, Artificial/ (13395) 14 exp Pacemaker, Artificial/ (17098) 15 exp Cardiomyopathy, Dilated/ (8550) 16 Heart-Assist Devices/ (4254) 17 exp Heart Conduction System/ (29066) 18 exp Arrhythmia/ (111066) 19 exp Ventricular Remodeling/ (2064) 20 Bundle-Branch Block/ (5690) 21 exp Heart Failure, Congestive/ (54150) 22 exp Ventricular Dysfunction, Left/ (8340) 23 (heart adj3 failure).mp. (71019) 24 (chf or chronic heart failur$).ti,ab. (9352) 25 chronic cardiac failure$.ti,ab. (311) 26 ((cardiac or ventricular or intraventricular) adj5 asynchron$).ti,ab. (290) 27 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).ti,ab. (113) 28 or/13-27 (209810) 29 12 and 28 (1090) 30 limit 29 to humans (1052) 31 exp ECONOMICS/ (342050) 32 exp ECONOMICS, HOSPITAL/ (13570) 33 exp ECONOMICS, PHARMACEUTICAL/ (1533) 34 exp ECONOMICS, NURSING/ (3648) 35 exp ECONOMICS, DENTAL/ (3281) 36 exp ECONOMICS, MEDICAL/ (9710) 37 exp "Costs and Cost Analysis"/ (119082) 38 VALUE OF LIFE/ (4582) 39 exp MODELS, ECONOMIC/ (4516) 40 exp FEES/ and CHARGES/ (6769) 41 exp BUDGETS/ (8961) 42 (economic$ or price$ or pricing or pharmacoeconomic$ or pharma economic$).tw. (76500) 43 (cost$ or costly or costing$ or costed).tw. (167635) 44 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. (10352) 45 (expenditure$ not energy).tw. (9242) 46 (value adj2 (money or monetary)).tw. (507) 47 budget$.tw. (9583) 48 (economic adj2 burden).tw. (1123) 49 "resource use".ti,ab. (1721) 50 or/31-49 (491055) 51 letter.pt. (542860) 52 editorial.pt. (180998)

continued

Databases and years searched	Date searched and search files
	53 comment.pt. (285878) 54 or/51-53 (761527) 55 50 not 54 (459858) 56 30 and 55 (49) 57 limit 56 to english language (40)
EMBASE 1980 to 2006 Week 1 Searched 13 January 2006	1 (CRT or "cardiac resynchron$ therap$").ti,ab. (2039) 2 resynchron$ therap$.ti,ab. (515) 3 BVP.ti,ab. (99) 4 cardiac resynchronization therapy/ (480) 5 (biventricular adj10 pac$).mp. (601) 6 (biventricular adj10 stimulat$).mp. (113) 7 ((cardiac or heart) adj10 resynch$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (852) 8 (coronary adj10 resynch$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (45) 9 (atriobiventricular adj10 pac$).mp. (9) 10 CRT-P.mp. (32) 11 CRT-D.mp. (9) 12 (insync or contak or "epic hf" or ovatio or situs or "newliving" or alto).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2229) 13 or/1-12 (5076) 14 exp Cardiac Pacing, Artificial/ (9969) 15 exp Pacemaker, Artificial/ (7728) 16 exp Cardiomyopathy, Dilated/ (5317) 17 Heart-Assist Devices/ (1657) 18 exp Heart Conduction System/ (8870) 19 exp Arrhythmia/ (118142) 20 exp Ventricular Remodeling/ (3113) 21 Bundle-Branch Block/ (752) 22 exp Heart Failure/ (85224) 23 exp Heart Failure, Congestive/ (20888) 24 exp Ventricular Dysfunction, Left/ (10453) 25 (heart adj3 failure).mp. (77282) 26 (chf or chronic heart failur$).ti,ab. (9496) 27 chronic cardiac failure$.ti,ab. (250) 28 ((cardiac or ventricular or intraventricular) adj5 asynchron$).ti,ab. (335) 29 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).ti,ab. (137) 30 or/14-29 (217519) 31 13 and 30 (1334) 32 limit 31 to humans (1264) 53 (cost$ adj2 effective$).ti,ab. (33343) 54 (cost$ adj2 benefit$).ti,ab. (8147) 55 cost-effectiveness analysis/ (41244) 56 cost benefit analysis/ (22327) 57 budget$.ti,ab. (7098) 58 cost$.ti. (31187) 59 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (37300) 60 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (12128) 61 (price$ or pricing$).ti,ab. (8918) 62 (financial or finance or finances or financed).ti,ab. (18425) 63 (fee or fees).ti,ab. (4324) 64 cost/ (17971) 65 cost minimization analysis/ (904) 66 cost of illness/ (2859) 67 cost utility analysis/ (1495) 68 drug cost/ (25437) 69 health care cost/ (44871)

continued

Databases and years searched	Date searched and search files
	70 health economics/ (8060) 71 economic evaluation/ (2821) 72 economics/ (4745) 73 pharmacoeconomics/ (850) 74 budget/ (6230) 75 economic burden.ti,ab. (1118) 76 "resource use".ti,ab. (18087) 77 or/53-76 (201835) 78 (editorial or letter).pt. (452160) 79 77 not 78 (181984) 80 79 and 32 (87) 81 limit 80 to english language (72)
PreMEDLINE Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 9 January 2006	Combined with PreMedline search line 19 23 (economic$ or price$ or pricing or pharmacoeconomic$ or pharma economic$).tw. (2899) 24 (cost$ or budget$).tw. (6006) 25 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. (335) 26 (value adj2 (money or monetary)).tw. (19) 27 23 or 24 or 25 or 26 (8131) 28 27 and 19 (7)
Science Citation Index	23 (economic* or price* or pricing or pharmacoeconomic* or pharma economic*) 24 (cost* or budget*). 25 (cost* SAME (benefit* or utility* or minim*)) 26 (value SAME (money or monetary)) 27 23 or 24 or 25 or 26 Combined with SCI core above
Web of Science Proceedings	23 (economic* or price* or pricing or pharmacoeconomic* or pharma economic*) 24 (cost* or budget*). 25 (cost* SAME (benefit* or utility* or minim*)) 26 (value SAME (money or monetary)) 27 23 or 24 or 25 or 26 Combined with SCI core above
NHS EED	See above
Econlit	heart failure

Epidemiology searches

Databases and years searched	Date searched and search files
MEDLINE (OVID) 1966 to November Week 3 2005	1 *Heart Failure/ (55601) 2 *INCIDENCE/ (1878) 3 *PREVALENCE/ (2719) 4 *risk factor/ (10247) 5 *prognosis/ (6738) 6 *ETIOLOGY/ (520) 7 2 or 3 or 4 or 5 or 6 (21560) 8 1 and 7 (80) 9 incidence.ti. (42317) 10 prevalence.ti. (39923) 11 *epidemiology/ (3747) 12 12 or 13 or 14 (84719) 13 1 and 12 (178) 14 (natural adj2 history).ti,ab. (21112) 15 14 and 2 (137) 16 8 or 13 or 15 (291)
EMBASE (OVID) 1980 to 2005 Week 48	1 *Heart Failure/ (24154) 2 *INCIDENCE/ (1523) 3 *PREVALENCE/ (2257) 4 *risk factor/ (9611) 5 *prognosis/ (6011) 6 *ETIOLOGY/ (520) 7 2 or 3 or 4 or 5 or 6 (19479) 8 1 and 7 (77) 9 incidence.ti. (27088) 10 prevalence.ti. (29979) 11 *epidemiology/ (9117) 12 or/9-11 (64836) 13 1 and 12 (128) 14 (natural adj2 history).ti,ab. ((18318)) 15 14 and 2 (47) 16 8 or 13 or 15 (241)
Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 5 December 2005	1 incidence.ti. (829) 2 prevalence.ti. (1267) 3 prognosis.mp. [mp=title, original title, abstract, name of substance word] (3372) 4 etiology.mp. [mp=title, original title, abstract, name of substance word] (1776) 5 (natural adj2 history).mp. [mp=title, original title, abstract, name of substance word] (532) 6 risk$.mp. [mp=title, original title, abstract, name of substance word] (21325) 7 or/1-6 (27146) 8 heart failure$.mp. [mp=title, original title, abstract, name of substance word] (2034) 9 7 and 8 (593) 10 or/1-5 (7544) 11 8 and 10 (206) 12 from 11 keep 2 (1) 13 limit 12 to english language (1) 14 11 (206) 15 limit 14 to english language (169)

Quality of life searches

Databases and years searched	Date searched and search files
Ovid MEDLINE(R) 1966 to December Week 4 2005 Searched 11 January 2006	Combined with Line 30 Clinical effectiveness search 59 "Quality of Life"/ (49829) 60 value of life/ (4582) 61 quality adjusted life year/ (2346) 62 quality adjusted life.ti,ab. (1645) 63 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (1292) 64 disability adjusted life.ti,ab. (288) 65 daly$.ti,ab. (365) 66 health status indicators/ (9694) 67 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (4837) 68 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (621) 69 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (546) 70 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (14) 71 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (251) 72 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (693) 73 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (1638) 74 (hye or hyes).ti,ab. (44) 75 health$ year$ equivalent$.ti,ab. (30) 76 health utilit$.ab. (291) 77 (hui or hui1 or hui2 or hui3).ti,ab. (328) 78 disutil$.ti,ab. (58) 79 rosser.ti,ab. (55) 80 quality of well being.ti,ab. (178) 81 quality of wellbeing.ti,ab. (1) 82 qwb.ti,ab. (98) 83 willingness to pay.ti,ab. (642) 84 standard gamble$.ti,ab. (366) 85 time trade off.ti,ab. (311) 86 time tradeoff.ti,ab. (115) 87 tto.ti,ab. (207) 88 or/60-87 (25065) 89 letter.pt. (542860) 90 editorial.pt. (180998) 91 comment.pt. (285878) 92 or/89-91 (761527) 93 88 not 92 (23890) 94 93 and 30 (5) 95 limit 94 to english language (5)
EMBASE 1980 to 2006 Week 1 Searched 13 January 2006	Combined with Line 31 CE search 83 exp "quality of life"/ (62436) 84 quality adjusted life year/ (2269) 85 quality adjusted life.ti,ab. (1634) 86 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (1239) 87 disability adjusted life.ti,ab. (265) 88 daly$.ti,ab. (308) 89 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (4826)

continued

Databases and years searched	Date searched and search files
	90 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (743) 91 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (538) 92 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (22) 93 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (176) 94 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (711) 95 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (1632) 96 (hye or hyes).ti,ab. (25) 97 health$ year$ equivalent$.ti,ab. (22) 98 health utilit$.ab. (289) 99 (hui or hui1 or hui2 or hui3).ti,ab. (256) 100 disutil$.ti,ab. (64) 101 rosser.ti,ab. (45) 102 quality of well being.ti,ab. (499) 103 quality of wellbeing.ti,ab. (6) 104 qwb.ti,ab. (89) 105 willingness to pay.ti,ab. (630) 106 standard gamble$.ti,ab. (334) 107 time trade off.ti,ab. (311) 108 time tradeoff.ti,ab. (109) 109 tto.ti,ab. (222) 110 (index adj2 well being).mp. (1273) 111 (quality adj2 well being).mp. (2592) 112 (health adj3 utilit$ ind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (219) 113 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (133) 114 quality adjusted life year$.mp. (2840) 115 (15D or 15 dimension$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (481) 116 (12D or 12 dimension$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (164) 117 rating scale$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (45069) 118 linear scal$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (234) 119 linear analog$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (618) 120 visual analog$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (13995) 121 (categor$ adj2 scal$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (730) 122 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 (123184) 123 (letter or editorial or comment).pt. (452160) 124 122 not 123 (116126) 125 124 and 32 (167) 126 limit 125 to english language (148)
Pre-MEDLINE Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 9 January 2006	30 quality of life.mp. (2472) 36 quality adjusted life.ti,ab. (104) 37 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (101) 38 disability adjusted life.ti,ab. (26)

continued

Databases and years searched	Date searched and search files
	39 daly$.ti,ab. (24) 40 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (336) 41 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (61) 42 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (51) 43 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (0) 44 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (0) 45 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (62) 46 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (130) 47 (hye or hyes).ti,ab. (0) 48 health$ year$ equivalent$.ti,ab. (1) 49 health utilit$.ab. (19) 50 (hui or hui1 or hui2 or hui3).ti,ab. (28) 51 disutil$.ti,ab. (2) 52 rosser.ti,ab. (1) 53 quality of well being.ti,ab. (7) 54 quality of wellbeing.ti,ab. (0) 55 qwb.ti,ab. (1) 56 willingness to pay.ti,ab. (50) 57 standard gamble$.ti,ab. (9) 58 time trade off.ti,ab. (8) 59 time tradeoff.ti,ab. (5) 60 tto.ti,ab. (11) 61 (index adj2 well being).mp. (7) 62 (quality adj2 well being).mp. (22) 63 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word] (15) 64 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance word] (4) 65 quality adjusted life year$.mp. (100) 66 (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word] (36) 67 (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word] (13) 68 rating scale$.mp. [mp=title, original title, abstract, name of substance word] (519) 69 linear scal$.mp. [mp=title, original title, abstract, name of substance word] (74) 70 linear analog$.mp. [mp=title, original title, abstract, name of substance word] (21) 71 visual analog$.mp. [mp=title, original title, abstract, name of substance word] (480) 72 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance word] (24) 73 or/36-72 (1890) 74 (letter or editorial or comment).pt. (19339) 75 73 not 74 (1878) 76 75 and 19 (3)
Science Citation Index	30 quality of life.mp. (2472) 36 quality adjusted life.ti,ab. (104) 37 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (101) 38 disability adjusted life.ti,ab. (26) 39 daly$.ti,ab Combined with line 21

Adverse effects/safety searches

Databases and years searched	Date searched and search files
Ovid MEDLINE(R) 1966 to December Week 4 2005	1 (CRT or "cardiac resynchron$ therap$").ti,ab. (2173) 2 resynchron$ therap$.ti,ab. (455) 3 BVP.ti,ab. (110) 4 (biventricular adj10 pac$).mp. (566) 5 (biventricular adj10 stimulat$).mp. (84) 6 ((cardiac or heart) adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (532) 7 (coronary adj10 resynch$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (20) 8 (atriobiventricular adj10 pac$).mp. (7) 9 CRT-P.mp. (30) 10 CRT-D.mp. (4) 11 (insync or contak or "epic hf" or ovatio or situs or "newliving" or alto).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3360) 12 or/1-11 (6148) 13 exp Cardiac Pacing, Artificial/ (13395) 14 exp Pacemaker, Artificial/ (17098) 15 exp Cardiomyopathy, Dilated/ (8550) 16 Heart-Assist Devices/ (4254) 17 exp Heart Conduction System/ (29066) 18 exp Arrhythmia/ (111066) 19 exp Ventricular Remodeling/ (2064) 20 Bundle-Branch Block/ (5690) 21 exp Heart Failure, Congestive/ (54150) 22 exp Ventricular Dysfunction, Left/ (8340) 23 (heart adj3 failure).mp. (71019) 24 (chf or chronic heart failur$).ti,ab. (9352) 25 chronic cardiac failure$.ti,ab. (311) 26 ((cardiac or ventricular or intraventricular) adj5 asynchron$).ti,ab. (290) 27 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).ti,ab. (113) 28 or/13-27 (209810) 29 12 and 28 (1090) 30 limit 29 to humans (1052) 31 adverse effect$.mp. (49247) 32 exp risk/ (412943) 33 exp causality/ (279567) 34 side effect$.mp. (103248) 35 harm.mp. (8167) 36 contraindicat$.mp. (18009) 37 (safe$ or safety).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (237068) 38 (cause or causation or causing or causal).mp. (427452) 39 risk.mp. (710215) 40 or/31-39 (1398132) 41 30 and 40 (271) 42 limit 41 to english language (218)
EMBASE 1980 to 2006 Week 1 Searched 13 January 2006	128 adverse effect$.mp. (47539) 129 exp risk/ (380742) 130 exp causality/ (571078) 131 side effect$.mp. (150321) 132 harm.mp. (7250) 133 contraindicat$.mp. (29095) 134 (safe$ or safety).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (264166) 135 (cause or causation or causing or causal).mp. (377835)

continued

Databases and years searched	Date searched and search files		
	136 risk.mp. (645278) 137 or/128-136 (1665080) 138 137 and 32 (501) (combined with CE final set)		
SCI-EXPANDED 1970–2006 English limited	#18	66	#17 and #13 *DocType=All document types; Language=English;* *Database=SCI-EXPANDED; Timespan=1970-2006*
	#17	>100,000	#16 OR #15 OR #14 *DocType=All document types; Language=All languages;* *Database=SCI-EXPANDED; Timespan=1970-2006*
	#16	>100,000	TS=((safe* or safety)) *DocType=All document types; Language=All languages;* *Database=SCI-EXPANDED; Timespan=1970-2006*
	#15	40,583	TS=(adverse effect*) *DocType=All document types; Language=All languages;* *Database=SCI-EXPANDED; Timespan=1970-2006*
	#14	62,159	TS=(side effect*)
Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations 9 January 2006 Searched 11 January 2006	79 adverse effect$.mp. (1617) 82 side effect$.mp. (2570) 83 harm.mp. (465) 84 contraindicat$.mp. (498) 85 (safe$ or safety).mp. [mp=title, original title, abstract, name of substance word] (8387) 86 (cause or causation or causing or causal).mp. (12633) 87 risk.mp. (18642) 88 or/79-87 (39057) 89 88 and 19 (27) (Combined with core search)		

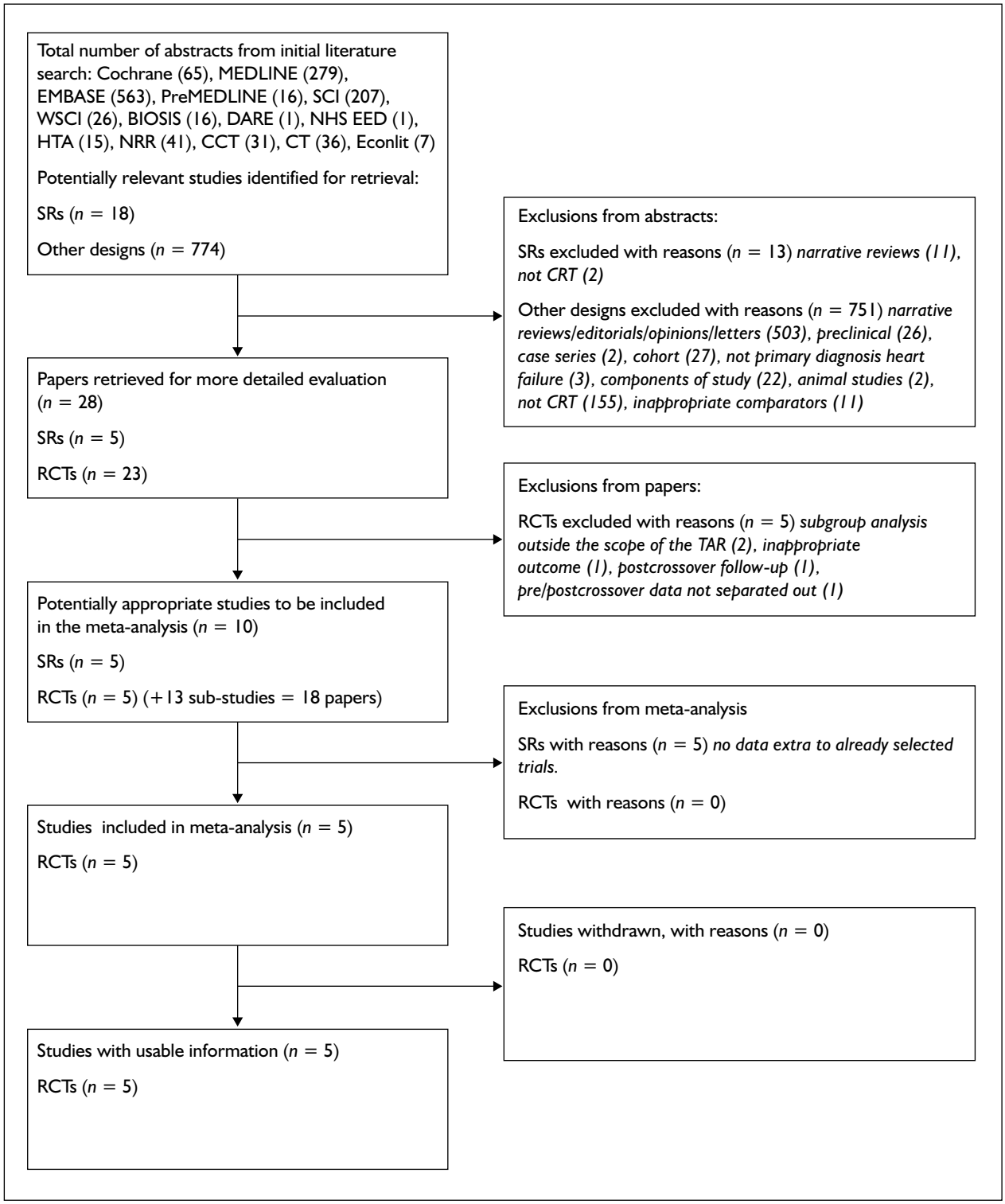
Non-English RCTS

Databases and years searched	Date searched and search files
Ovid MEDLINE(R) 1966 to December Week 4 2005 Searched 10 January 2006	Clinical effectiveness search run – non-English RCTs saved separately
EMBASE 1980 to 2006 Week 1	Clinical effectiveness search run – non-English RCTs saved separately

Appendix 2

Quality assessment

QUOROM statement flow diagram for the quality of studies in this TAR



Quality assessment using QUOROM framework: systematic reviews

Title

Bradley DJ, *et al*. (2003). Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;**289**:730–40

Meta-analysis based on systematic review of RCTs

Abstract

Uses a structured format?

Background:	Yes
Objectives:	Yes
Search strategy:	Yes
Selection criteria:	Yes
Data collection and analysis:	Yes
Main results:	Pooled results reported
Reviewers' conclusions:	Reports results

Introduction

Detailed introduction that includes description of health problem, current treatment options and a brief overview of CRT

Methods

Searching:	Number of electronic databases searched (search strategies provided) plus FDA website and handsearching of major cardiac journal and annual conference abstracts. Unpublished data sought from authors. Searches up to June 2002
Selection:	Inclusion and exclusion criteria listed. Note scope of review beyond CRT-P and CRT-D (included ICDs as comparator). Included RCTs only
Validity assessment:	Reported internal validity quality by category
Data abstraction:	Undertaken using standard forms by a two unblinded reviewers independently
Study characteristics:	Tables of study characteristics – patients, intervention and comparator
Quantitative data synthesis:	Binary outcomes summarised as odds ratios and pooled using random effect meta-analysis (sensitivity analysis for fixed effects). Statistical heterogeneity assessed

Results

Trial flow:	Flow diagram for study inclusion included
Study characteristics:	Table of study characteristics
Quantitative data synthesis:	Meta-analysis for all outcomes reported together with corresponding Forest plots. Sensitivity analyses undertaken to assess effect of CRT of ICD vs no trials trials and NYHA II–IV vs III–IV and trial selection

Discussion

The discussion summarises key findings, and discussed in the context of the potential limitations of the systematic review/meta-analysis. Future research agenda are suggested

Title

Pichon-Riviere, *et al*. (2005). *Cardiac resynchronization therapy: biventricular or tricameral pacemaker*. Instituto de Efectividad Clinica de Sanitaria, Buenos Aires, Argentina

Health technology assessment – systematic review

Introduction

Introduction that includes a brief description of health problem, current treatment options and overview of CRT

Methods

Searching:	Number of electronic databases searched (search strategies not provided) plus HTA websites. Search cut-off date not reported
Selection:	Limited inclusion and exclusion criteria listed
Validity assessment:	Not reported
Data abstraction:	Not reported
Study characteristics:	Limited tabular summary of study characteristics
Quantitative data synthesis:	Narrative

Results

Trial flow:	Not reported
Study characteristics:	Limited tabular summary of study characteristics
Quantitative data synthesis:	Narrative summary of each study

Discussion

The discussion summarises key findings and makes a grade of recommendation. Notes need for further long-term evidence. Definition of tricameral = 3-chamber

Title

McAlister F, *et al*. (2004). Cardiac resynchronization therapy for congestive heart failure. *Ann Intern Med* 2004;**141**:381–90[49] and McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, *et al*. Cardiac resynchronization therapy for congestive heart failure. *Evid Rep Technol Assess* (Summ). 2004 Nov. (106):1–8

Meta-analysis based on systematic review of RCTs

Abstract

Uses a structured format?

Background:	None
Objectives:	Yes
Search strategy:	Yes
Selection criteria:	Yes
Data collection and analysis:	Yes
Main results:	Pooled results reported
Reviewers' conclusions:	Reports results

Introduction

Detailed introduction that includes description of health problem, current treatment options and a brief overview of CRT

Methods

Searching:	Number of electronic databases searched (search strategies provided) plus FDA website. Unpublished data sought from manufacturers. Searches up to May 2004
Selection:	Detailed inclusion and exclusion criteria listed. Note scope of review beyond CRT-P and CRT-D (included double chamber and multisite pacers as interventions and univentricular pacing and ICDs as comparators). Included RCTs for efficacy and non-RCTs for safety
Validity assessment:	Assessed quality of RCTs using Jadad and safety studies using validated checklist. Reported quality by category as well as total quality checklist scores
Data abstraction:	Undertaken using standard forms by a single reviewer and checked by a second
Study characteristics:	Detailed tables of study characteristics – patients, intervention, comparator and outcome – used to assess clinical heterogeneity
Quantitative data synthesis:	Binary outcomes summarised as RRs and continuous outcomes (health-related QoL) as mean differences. Reported both fixed and random effect meta-analysis results. Heterogeneity explored using meta-regression

Results

Trial flow:	Flow diagram for study inclusion included
Study characteristics:	Detailed tables of study characteristics – patients, intervention, comparator and outcome – listed in report appendix
Quantitative data synthesis:	Meta-analysis for all efficacy and safety outcomes reported together with corresponding Forest plots. Report influence of inclusion of ICD on efficacy outcomes using meta-regression

Discussion

The discussion summarises key findings, and discussed in the context of internal and external validity. The limitations of both the included trials and systematic review/meta-analysis are presented. No future research agenda is suggested

Notes

The inclusion criteria for the review include multisite pacing and dual chamber pacing and also allow for univentricular pacing as a comparator

Title

Freemantle N, *et al*. (2006). Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction – a systematic review and meta-analysis. *Eur J Heart Fail* 2006;**8**:433–40

Systematic review and meta-analysis

Abstract
Uses a structured format?

Background:	Yes
Objectives:	Yes
Search strategy:	No – reported as elsewhere
Selection criteria:	Yes; the scope of this review included trials that are beyond the scope of this TAR
Data collection and analysis:	Yes
Main results:	Results of CARE-HF, COMPANION, CONTAK-CD, MIRACLE, MIRACLE ICD, MUSTIC-SR, MUSTIC-AF, RD-CHF, reported
Reviewers' conclusions:	In form of a discussion

Introduction

Brief introduction giving background, methodology rationale and shortcomings of previous meta-analysis

Methods

Searching:	Strategy is not detailed in this paper
Selection:	Inclusion and exclusion criteria listed. Also included ICD and univentricular as comparators
Validity assessment:	No details given
Data abstraction:	By one reviewer and checked by another using a standard format
Study characteristics:	Tables of study characteristics – patients, intervention and comparator
Quantitative data synthesis:	Full and random effects analysis and meta-regression were used

Results

Trial flow:	None
Study characteristics:	Tables of characteristics and results of included studies
Quantitative data synthesis:	Presented as Forest plots and in the text

Discussion

The discussion summarises key findings and makes recommendations on use of CRT-P and CRT-D

Title

Abdulla J, *et al*. (2006). Impact of implantable defibrillators and resynchronization therapy on outcome in patients with left ventricular dysfunction – a meta-analysis. *Cardiology* 2006;**106**:249–55

Meta-analysis based on systematic review of RCTs

Abstract

Uses a structured format?

Background:	Yes
Objectives:	Yes
Search strategy:	Yes
Selection criteria:	Yes
Data collection and analysis:	Yes
Main results:	Pooled results reported
Reviewers' conclusions:	Reports results and need for further research

Introduction

Detailed introduction that includes description of health problem, current treatment options and a brief overview of CRT

Methods

Searching:	Number of electronic databases searched (search strategies provided) and handsearching of conference abstracts. Searches up to June 2005
Selection:	Inclusion and exclusion criteria listed. Note scope of review beyond CRT-P and CRT-D (included ICDs as intervention and univentricular pacing as comparator). Included RCTs and CCTs
Validity assessment:	No quality assessment undertaken
Data abstraction:	Undertaken using standard forms by three reviewers
Study characteristics:	Tables of study characteristics – patients, intervention and comparator
Quantitative data synthesis:	Binary and continuous outcomes summarised as odds ratios and weighted mean differences and pooled using random effect meta-analysis (sensitivity analysis for fixed effects). Statistical heterogeneity assessed

Results

Trial flow:	Details of selection given. No flow diagram
Study characteristics:	Limited details given in study characteristics table
Quantitative data synthesis:	Meta-analysis for all outcomes reported together with corresponding Forest plots. Separate meta-analyses for CRT and ICD trials

Discussion

The discussion summarises key findings, and discussed in the context of the potential limitations of the systematic review/meta-analysis. Concludes selective patients with LVSD benefit from CRT, ICD or both and further research necessary to clarify which patients benefit most from a single or combined device implantation

Appendix 3

Data extraction tables: randomised controlled trials

Study

Title: CARE-HF
- Cleland *et al*., 2001,[70] 2005[71,72,74] + study update[73]
- (Calvert *et al*., 2005, in SR of cost-effectiveness)

Country: Across Europe

Setting: Multiple, 82 centres across 12 countries including UK (n = 147)

Recruitment dates: January 2001 to March 2003

Study design: Parallel RCT

Subjects

Total number: 813 (C = 404, CRT-P = 409)

Inclusion criteria:
- ⩾18 years
- NYHA II–IV
- QRS interval ⩾120 ms
- LVEF ⩽35%
- LVEDD ⩾30 mm
- Optimal medical therapy
- Sinus rhythm
- HF symptoms >6 weeks

Exclusion criteria:
- Major CV event in previous 6 weeks
- Indications for pacemaker or ICD
- On i.v. treatment for HF
- Persistent AF or atrial flutter
- Cardiac surgery or other major events ⩽6 weeks
- Life expectancy <1 year

Subgroups:
Predefined:
- Age
- Sex
- NYHA class
- Presence of dilated cardiomyopathy
- SBP
- NT-BNP
- LVEF
- ESVI
- QRS
- Interventricular mechanical delay
- GFR
- On β-blockers
- On spironolactone
- On loop diuretics
- On digoxin

Intervention

Intervention:
CRT-P and optimal medical therapy
InSync, Medtronic

Comparator:
Optimal medical treatment including β-blockers and ACE inhibitors

Concurrent treatment:
None reported

Notes:

continued

Patient baseline characteristics
At randomisation

	Control	Intervention
N	404	409
Age mean (SD or range)[a] (years)	66 (59–72)	67 (60–73)
Male *n* (%)	293 (73)	304 (74)
Severity of HF		
Class I *n* (%)	0	0
Class II *n* (%)	0	0
Class III *n* (%)	376 (93)	386 (94)
Class IV *n* (%)	27 (7)	23 (6)
Cardiac dyssynchrony (QRS)		
Mean (SD or range)[a]	160 (152–180)	160 (152–180)
LVEF mean (SD or range)[a]	25 (22–29)	25 (21–29)
Ischaemic HD *n* (%)	144 (36)	165 (40)
β-Blocker *n* (%)	298 (74)	188 (70)
Spironolactone *n* (%)	238 (59)	219 (54)
Atrial fibrillation *n* (%)	0 (0)	0 (0)
ACE or angiotension blocker *n* (%)	383 (95)	387 (95)

[a] Medians and IQRs reported.

Outcome measures

Primary outcome measure:

- Combined outcome of all-cause mortality or unplanned hospitalisation for HF

Secondary measures:

- Non-HF mortality
- All-cause mortality
- HF hospitalisations
- Exercise capacity
- NYHA class before and after treatment
- Adverse events
- Health-related QoL

Method of assessing outcomes:
Clinical evaluations at baseline, 1, 3, 6, 9, 12, 18 months, then at 6-month intervals

Length of follow-up:
Main study: mean 29.4 months
Extension study: mean 36.4 months

Results

	Control			Intervention			RR or HR
	n	*N*		*n*	*N*		(95% CI or *p*-value)
Effectiveness outcomes							
At time to first event unless stated otherwise	56	404		33	409		Not reported
Progressive HF mortality	64	404		38	409		HR 0.55 (0.37 to 0.82)
Extension study							
Non-HF mortality	164	404		49	409		Not reported
All-cause mortality	120	404		82	409		HR 0.64 (0.48 to 0.85)
Extension study	154	404		101	404		HR 0.60 (0.47 to 0.77)
Sudden death	38	404		29	409		
Extension study	54	404		32	409		HR 0.54 (0.35 to 0.84)
HF hospitalisations							
People	133	404		72	409		HR 0.48 (0.36 to 0.64)
Events	384	404		222	409		
NYHA class I							
At 18 months	39	405		105	409		Not reported
NYHA class II							
At 18 months	112	405		150	409		Not reported
NYHA class III/IV							
At 18 months	152	405		80	409		Not reported
	N	**Mean**	**SD**	***N***	**Mean**	**SD**	**Mean difference (95% CI)**
NYHA							
At 90 days	404	2.7	0.9	409	2.1	1.0	0.6 (0.4 to 0.7)
Health-related QoL (EQ-5D)							
At 90 days[a]	404	0.60	0.20	409	0.60	0.20	
At 18 months	404	0.63	0.29	409	0.70	0.28	0.08 (0.04 to 0.12)
Health-related QoL (MLHFQ)							
At 90 days	404	40	22	409	31	22	–10 (–8 to –12)

Subgroups
Number of subgroups analysed (age; sex; NYHA class (III vs IV); LVEF; dilated cardiomyopathy; NT-BNP; ESVI; QRS interval; morphology (LBBB vs other); systolic BP; GFR; drug (ACE, β-blocker, loop diuretic, spinolacetone, digoxin) for primary outcome – none reported to be statistically significant

[a] Taken from Calvert paper for all patients, assumed equal across 2 groups

continued

	Control		Intervention		RR or HR (95% CI)
	n	***N***	***n***	***N***	
Adverse outcomes					
Worsening HF					
At 24 months [mean 29.4 months]	263	405	191	409	Not reported, $p < 0.001$
Atrial arrhythmias or ectopy					
At 24 months [mean 29.4 months]	41	405	64	409	Not reported, $p = 0.02$
Others					
Respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmias or ectopy and neurological events	Similar between two groups				

Device-specific adverse outcomes

Safety events (within 7 days of implant)	Intervention		Comments
	n	***N***	
Device or battery related[a]	8	409	Pocket erosion
	6	409	Pneumothorax
Lead related[a]	24	409	
Infection[a]	3	409	Device-related infection
Perforation or dissection[a]	10	409	Coronary-sinus dissection

Extension study crossover	Control		Intervention	
	n	***N***	***n***	***N***
Total number of implant failures	95	404	19	409

[a] Timing of events (peri- or postoperative) not stated

Methodological comments	
Prospective recruitment?	Yes
Selection/randomisation:	Unknown
Method of randomisation:	Not mentioned
Block:	No, but minimisation was used
Stratification:	Yes (NYHA class)
Concealment of allocation:	No
Groups similar at baseline?	Yes
Eligibility criteria stated?	Yes
Appropriate?	Yes
Blinding:	None Classification of primary outcomes and adverse events undertaken by blinded independent committee
Outcome measures:	Objective? Event outcomes objective and health-related QoL subjective
ITT: **If no, justified?**	Yes
Protocol violations specified:	No
Follow-up/attrition:	All people accounted for? Yes Withdrawal specified? Yes Withdrawal reasons given? Yes Were intervention and control groups followed-up similarly? Yes Were both groups treated similarly apart from the intervention? Yes
Data analysis:	Statistical tests used: Cox proportional hazards for events
Are they appropriate?	Yes
How were missing data accounted for?	No loss to follow-up or missing data reported

continued

Power calculation at design?	Yes on basis of 14% relative reduction in primary outcome
Does it justify any subgroup analyses carried out?	Yes, *pre-hoc* specification and stated to be exploratory only. Subgroups presented as stratified HRs and assessed by heterogeneity test
Are the conclusions supported by the results?	Yes
Was ethical approval given?	Yes
Generalisability:	834 potentially suitable patients had information sent to the core ECHO laboratory by investigators for possible inclusion in the study. 13 patients were rejected on the basis of lack of dyssynchrony and 8 patients were not randomised as they died during the run-in phase. 813 remaining patients were randomised. However, the study was unblinded and the method of randomisation unknown
Conflict of interest:	Trial supported by Medtronic and authors state conflicts
Inter-centre variability	Not discussed but taken into account in analysis which allowed for centre effects which was entered as a random covariate

General comments
- People were randomised prior to implant
- Baseline measures were taken at randomisation

Study

Title: COMPANION[75]
- Bristow *et al*., 2000, 2004[76]
- Carson *et al*., 2005[77]
- FDA report[78]

Ontario review 2005
Country: USA

Setting: Multiple, 128

Recruitment dates: January 2000–December 2002

Study design: Prospective, parallel, RCT

Participants
Total number: 1520 (C = 308, CRT-P = 617, CRT-D = 595)

Inclusion criteria:
- ⩾18 years
- NYHA III–IV
- Cardiac dyssynchrony QRS ⩾120 ms, PR interval >150 ms
- LVSD ⩽35%
- Optimal medical therapy
- LVEDD ⩽60 mm

Exclusion criteria:
- Bradycardia stimulation
- ICD indications
- Life expectancy <6 months
- Chronic atrial tachyarrhythmias
- Indications for antibradycardia pacing
- Unexplained syncope
- MI within 60 days of randomisation
- Uncontrolled blood pressure
- Surgically uncorrected primary valvular HD
- Progressive or unstable angina
- Pregnancy
- Hypertrophic obstructive cardiomyopathy
- Amyloid disease
- Tricuspid prosthesis
- Hospitalisation for HF >4 hours in previous month

Intervention
Intervention:
Optimal medical therapy and either
CRT-P
Guidant Model 1241 CONTAK-TR
or
CRT-D
Guidant Model 1823 CONTAK-CD

Leads
RA: Guidant Endotak 0125
RV: Guidant Endotak 0154
RV: for defibrillation: Guidant 0155
LV: Guidant Easytrak 4510–4513

Comparator:
Optimal medical therapy

Concurrent treatment:
None reported

Notes:
Randomisation was in a ratio 1:2:2 (control, CRT-P, CRT-D)

continued

Subgroups:
- Ischaemic HF
- Age
- Sex
- NYHA class
- LVDD
- Medical therapy

Patient baseline characteristics
At 1 week postimplant[a]

	Control	CRT-P	CRT-D
N	308	617	595
Age mean (SD or range)[a] (years)	68	67	66
Male *n* (%)	69	67	67
Severity of HF			
Class I (%)			
Class II (%)			
Class III (%)	82	87	86
Class IV (%)	18	13	14
Cardiac dyssynchrony (QRS)			
QRS (ms)	158	160	160
LVEF	0.22	0.20	0.22
Ischaemic HD (%)	59	54	55
β-Blocker (%)	66	68	68
Spironolactone (%)	55	53	55
ACE or angiotensin blocker (%)	89	89	90
Diabetes (%)	45	39	41
Left branch bundle block *n* (%)	70 (23)	69 (11)	73 (12)
Right branch bundle block *n* (%)	9 (3)	12 (2)	10 (2)

[a] Median values given for continuous measures. There were no significant differences between groups

Outcome measures
Primary outcome measure:
- All-cause mortality and all-cause hospitalisation

Secondary measures:
- Cardiac morbidity
- Cardiac hospitalisation
- All-cause mortality
- Exercise capacity – peak oxygen uptake (VO_2 max)
- Six-minute walk
- NYHA class before and after treatment
- Adverse events
- Health-related QoL, MLHFQ

Method of assessing outcomes:
Clinical evaluations at baseline, 1 week, 1 month, 3 months thereafter (postrandomisation)

Length of follow-up:
Data were collected at 3-month intervals postrandomisation

Median duration for primary end-point and ACM:
CRT-P 16.2 months
CRT-D 15.7 months
OPT 11.9 months

Results

	Optimal drug therapy		CRT-P		RR or HR (95% CI or *p*-value)	CRT-D		RR or HR (95% CI or *p*-value)
	n	*N*	*n*	*N*		*n*	*N*	
Effectiveness outcomes								
Analysed from time of randomisation to time of first event								
Progressive HF mortality	34	308	53	617		52	595	
Non-HF mortality	25	308	30	617		36	595	
All-cause mortality	77	308	131	617	HR 0.76 (0.58 to 1.01)	105	595	HR 0.64 (0.48 to 0.86)
HF hospitalisations (no. of events), 15.5 vs 12.1 months	216	308	ND[a]	617		314	595	
Sudden death	18	308	48	617		17	595	
Cardiac death	58	308	109	617		76	595	

Subgroups
Number of subgroup analyses undertaken (age; sex; aetiology) (ischaemic vs non-ischaemic); NYHA class (III vs IV); LVEF; LVEDD; QRS interval; morphology (LBBB vs other); heart rate; systolic BP; diastolic BP; drug (ACE, β-blocker, loop diuretic, spinolacetone) for primary outcome and all-cause mortality – none reported to be as statistically significant

[a] ND, no data available

continued

	Optimal drug therapy			CRT-P			CRT-D			Mean difference (95% CI)
	n	Mean change	SD	*n*	Mean change	SD	*n*	Mean change	SD	
6-minute walk										
At 3 months (m)	170	9	84	422	33	99	420	44	109	
At 6 months (m)	142	1	93	373	40	96	378	46	98	
NYHA										
Improvement in class at 3 months (%)	242	24		551	58		543	55		
Improvement in class at 6 months(%)	199	38		489	61		497	57		
Health-related QoL (MLHFQ)										
Increase at 3 months	243	–9	21	510	–24	27	514	–24	28	
Increase at 6 months	207	–12	23	460	–25	26	478	–26	28	

	Control		CRT-P		CRT-D		RR or HR (95% CI)
	n (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	
Adverse outcomes							
Worsening HF							
At 6 months							
Atrial arrhythmias or ectopy							
At 6 months							
Deaths related to procedural complications							
n (%)			5 (0.8)	617	3 (0.5)	595	
All-cause moderate/severe adverse events							
At 6 months	188 (61)	308	407 (66)	617	411 (69)	595	
Others							

	CRT-P		CRT-D		Comments
	n (%)	*N*	*n* (%)	*N*	
Device specific adverse outcomes					
Safety perioperative events (within 7 days of implant)					
Implant procedure					
Including perforation or dissection	62 (10)	617	48 (8)	595	
Safety postoperative events (>8 days after implant)					
Device or battery related					
Lead related					
Implant procedure or tools					
Heart function					
Infection					
Perforation or dissection					
Numbers of failed implants	78 (13)	617	54 (9)	595	

Withdrawals[a]	Control		CRT-P		CRT-D		RR or HR (95% CI)
	n	*N*	*n*	*N*	*n*	*N*	
Reached primary end-point *n* (%)	80 (26)	308	37 (6)	617	42 (7)	595	
Did not reach primary end-point *n* (%)	40 (13)	308	12 (2)	617	12 (2)	595	

[a] Predominantly crossovers

continued

Methodological comments	
Prospective recruitment?	Yes
Selection/randomisation:	Unknown
Method of randomisation:	Not mentioned
Block:	Not mentioned
Stratification:	Yes, for β-blockers
Concealment of allocation:	Not mentioned
Groups similar at baseline?	Yes
Eligibility criteria stated?	Yes
Appropriate?	Yes
Blinding:	None
Outcome measures:	Objective? Yes
ITT:	Yes
If no, justified?	
Protocol violations specified:	No
Follow-up/attrition:	All people accounted for? Yes Withdrawal specified? Yes Withdrawal reasons given? Not clearly described Were intervention and control groups followed-up similarly? Yes Were both groups treated similarly apart from the intervention? Yes
Data analysis:	Statistical tests used: Efficacy analyses used the log-rank statistic for differences between groups and Kaplan–Meier analysis for survival data Subgroup analyses used the Wald χ^2 statistic Baseline differences were evaluated with the Wilcoxon rank-sum test for continuous and ordered data and Pearson's χ^2 test was used for categorical data
Are they appropriate?	Yes
How were missing data accounted for?	Individuals who withdrew (due to crossover or other reason) and for whom no primary outcome was available were regarded as censored.
Power calculation at design? **Does it justify any subgroup analyses carried out?**	Yes. Powered on total $N = 2200$ participants but stopped early at 1638 participants. It was agreed that 1000 primary end-points had been reached. No justification for choice of subgroups given. Present stratified HRs and use interaction tests
Are the conclusions supported by the results?	Yes
Was ethical approval given?	Not mentioned
Generalisability:	As the method of randomisation is not declared and the study unblinded, it is not possible to say whether the results are generalisable
Conflict of interest:	Yes, some investigators were supported financially by device manufacturers
Inter-centre variability	Not mentioned

General comments

- FDA report notes three changes in the definition of heart failure hospitalisation outcome over the duration of the trial
- Patients were randomised prior to implant
- First measures postimplant were taken at 1 week

Study

Title: CONTAK-CD
- Phase I preliminary data, Lozano *et al*., 2000[80]
- Saxon *et al*., 1999[79]
- Phase I and II Higgins *et al*., 2003[81]
- Knight *et al*., 2004[82]
- FDA report[83]
- Personal communication: Yong P, Guidant

Country: Phase I: USA, Europe and Australia
Phase II: USA

Setting: Multiple, 47 locations

Recruitment dates: February 1998–December 2000

Study design: Phase I: crossover RCT
Phase II: parallel RCT

Participants

Total number: 581 enrolled (567 implanted, 501 randomised)
Phase I: $n = 222$ (intervention = 109, control = 113)
Phase II: $n = 279$

Inclusion criteria:
- Age ⩾18 years
- NYHA II–IV
- Cardiac dyssynchrony QRS ⩾120 ms, PR interval >160 ms
- LVSD ⩽35%
- Indications for an ICD – ventricular tachyarrhythmia

Exclusion criteria:
- Atrial fibrillation/flutter within 6 months
- Indications for a permanent pacemaker
- Life expectancy <6 months from other conditions
- History of VT/VF

Subgroups: none specified

Patient baseline characteristics
At time of implant (pre-randomisation)

	Control ($n = 245$)	Intervention ($n = 245$)
Age (years)	66 ± 11	60 ± 11
Male (%)	83	85
Severity of HF		
Class I (%)	0	0
Class II (%)	33	54
Class III (%)	57	32
Class IV (%)	10	14
Cardiac dyssynchrony (QRS)		
Mean (SD or range)	156 ± 26	160 ± 27
LVEF mean (SD or range)	22 ± 7	21 ± 7
Ischaemic disease (%)	71	67
β-Blocker (%)	46	48
Spironolactone (%)	83	88
ACE (%)	89	86
Left branch bundle block *n/N* (%)	253/443 (57)	
Right branch bundle block *n/N* (%)	58/443 (13)	

Intervention
Intervention:
Optimal medical therapy and CRT-D
Pulse generator
Model 1822 Ventak CHK Automatic Implantable Cardioverter Defibrillator
or
Model 1823 Contak-CD device, Guidant, St Paul, MN, USA

Leads
LV: Model 4965 CapSure Epi pace/sense lead, Medtronic, Minneapolis, MN, USA
or
Model 4510/4511/4512/4513 Easytrak coronary venous pace/sense lead, Guidant

RV: Model 0125 Endotak lead, Guidant

LA: a pace/sense lead

Comparator:
CRT capacity turned off and optimal medical treatment

Concurrent treatment:
None reported

Notes:

Outcome measures
Phase I
Primary outcome measure:
- Progressive HF mortality

Secondary measures:
- Non-HF mortality
- All-cause mortality
- HF hospitalisations
- Exercise capacity
- NYHA class before and after treatment
- Adverse events
- Health-related QoL

Method of assessing outcomes:
Clinical evaluations at baseline, 3 and 6 months

Length of follow-up:
6 months

Analysis was limited to the crossover point at 3 months

continued

Phase I at time of randomisation – 30+ days postimplant

	Control	Intervention	Total
N	113	109	222
Age mean (SD or range) (years)			65 ± 10
Male (%)			83
Severity of HF			
Class I (%)			0
Class II (%)			35
Class III (%)			57
Class IV (%)			8
Cardiac dyssynchrony (QRS)			
Mean (SD or range)			
LVEF Mean (SD or range)			0.22 ± 0.07
Ischaemic HD (%)			68
β-Blocker (%)			38
Diuretics			83
Digoxin			66
ACE or angiotension blocker (%)			87

Phase I and II at time of randomisation – 30+ days postimplant (NYHA class III/IV only)

	Control (*n* = 110)	Intervention (*n* = 117)
Age (years)	66 ± 11	66 ± 11
Male (%)	78	77
Severity of HF		
Class II (%)	10	17
Class III (%)	71	73
Class IV (%)	19	10
Cardiac dyssynchrony (QRS)		
Mean (SD or range)	152 ± 26	164 ± 27
LVEF mean (SD or range)	21 ± 6	21 ± 6
Ischaemic disease (%)	71	65
β-Blocker (%)	40	45
Diuretics (%)	86	92
ACE (%)	89	81

Phase II

Primary outcome measure:

- All-cause mortality, hospitalisation for worsening HF and ventricular tachyarrhythmia needing device therapy

Secondary measures:

- Peak VO_2
- 6-minute walk test
- MLHFQ
- NYHA class
- LVID
- LVEF
- Adverse events

Covariates:

- NYHA class
- QRS interval
- Ischaemic aetiology
- LVEF
- Bundle branch morphology

Method of assessing outcomes:

Clinical evaluations at baseline, 3 and 6 months

Length of follow-up:

6 months

Results

Phase I

	Control *n*	Control *N*	Intervention *n*	Intervention *N*	RR or HR (95% CI or *p*-value)
Effectiveness outcomes					
HF mortality – pump failure n *(%)*					
At 3 months	7	113	2	109	
HF mortality – arrhythmic n *(%)*					
At 3 months	1	113	0	109	
Non-HF mortality n *(%)*					
At 3 months	1	113	2	109	
Unknown mortality n *(%)*					
At 3 months	1	113	1	109	
All-cause mortality[a] n *(%)*					
At 3 months	10	113	5	109	
Kaplan–Meier survival rate % (SD)	86 (0.6)	113	93 (0.4)	113	Log rank $p = 0.18$

[a] Kaplan–Meier curves available

continued

Phase I and II combined 3- and 6-month data

	Control		Intervention		RR or HR (95% CI or *p*-value)
	n	***N***	***n***	***N***	
Effectiveness outcomes					
All-cause mortality	16	245	11	245	
Sudden death	0	245	0	245	
Death due to HF	9	245	4	245	
HF hospitalisations					
People	39	245	32	245	
VT/VF	⩾1		⩾1		
Relative reduction in composite HF progression (%)			15		$p = 0.35$
Stratified by NYHA class I/II			12		
Stratified by NYHA class III/IV			22		
6-minute walk (m)	15	224	35	220	$p = 0.043$
NYHA class – time of implant (%)					
Class I	0	245	0	245	
Class II	33	245	32	245	
Class III	57	245	60	245	
Class IV	10	245	8	245	
NYHA class baseline – time of randomisation – 30+ days postimplant (%)					
Class I	0	110	0	117	
Class II	10	110	17	117	
Class III	71	110	73	117	
Class IV	19	110	10	117	
NYHA class (%)					
Improved 2 classes	2	116	11	109	
Improved 1 class	30	116	25	109	
No change	51	116	51	109	
Worsened	17	116	13	109	

	N	**Mean**	**SD**	***N***	**Mean**	**SD**	**Mean difference (95% CI)**
NYHA class							
At baseline time of implant							
At baseline time of randomisation – 30+ days postimplant							
Health-related QoL (MLHFQ)							
At 6 months	225	5	2	234	–7	2	

Adverse outcomes

Postoperative recovery (within 30 days of implant) prior to randomisation	10 deaths: 2 perioperative 5 pump failure 2 other cardiac causes 1 unknown 1 withdrawal	
Postrandomisation adverse events (data from people who had coronary venous leads n = 448)		
System infections (*n*/patients)	7/448	3 explanted, 4 treated with antibiotics
Surgical interventions to correct LV loss of pacing	29/448	
Surgical interventions to correct RV loss of pacing	3/448	
Surgical interventions to correct RA loss of pacing	5/448	
Battery replacements	1/448	
Coronary venous trauma (*n*/procedures)	1/517	
Transient AV block	0/517	
Hematoma	4/517	
Pneumothorax	4/517	

continued

Postsurgical wound pain	1/517
Renal failure	1/517

Cause and frequency of temporary and permanent loss of CRT during follow up N = *443* n *(%)*	CRT-D interrupted	CRT-D restored	CRT-D permanently lost
Atrial tachyarrhythmia	81 (18)	79 (18)	2 (0.5)
Loss of left ventricular capture	44 (10)	39 (9)	5 (1)
Extracardiac stimulation	11 (2)	6 (1)	5 (1)
Loss of right ventricular capture	9 (2)	9 (2)	0
Infection/pericarditis	5 (1)	2 (0.5)	3 (1)
Patient intolerance	5 (1)	1 (0.2)	4 (1)
Loss of right atrial sensing	5 (1)	5 (1)	0
Ventricular oversensing	1 (0.2)	0	1 (0.2)

Drop-outs
14 withdrawals from 581 enrolled
66 did not receive CRT because the coronary venous lead could not be placed (501 people were implanted with a CRT-D device)

Methodological comments

Prospective recruitment?	Yes
Selection/randomisation:	Method of randomisation unknown
Method of randomisation:	
Block:	Yes
Stratification:	Yes by NYHA class I and II and class III and IV
Concealment of allocation:	Not known
Groups similar at baseline?	Yes
Eligibility criteria stated?	Yes
Appropriate?	Yes
Blinding:	Double, does not say who
Outcome measures:	Objective? Yes, plus QoL and NYHA
ITT:	No, 'as therapy' except for operative mortality (personal communication)
If no, justified?	
Protocol violations specified:	No
Follow-up/attrition:	All people accounted for? No Withdrawal specified? Yes, in some cases Withdrawal reasons given? Yes, in some cases Were intervention and control groups followed-up similarly? Yes Were both groups treated similarly apart from the intervention? Yes
Data analysis:	Statistical tests used: • Cox proportional hazards models for the combination of events with treatment effect adjusted for covariates • Wei method used to calculate composite effect of treatment and covariates • Repeated measures for continuous variables • Maximum likelihood for estimating the model parameters
Are they appropriate?	Yes
How were missing data accounted for?	Not mentioned
Power calculation at design?	Not mentioned
Does it justify any subgroup analyses carried out?	No
Are the conclusions supported by the results?	Yes
Was ethical approval given?	Not reported
Generalisability:	Not enough information given about randomisation and blinding to make a judgement
Conflict of interest:	Supported by the Guidant
Inter-centre variability	Not mentioned

General comments
- People were randomised 2 weeks after implant
- A postimplant recovery period of a minimum of 30 days occurred before CRT was activated

Study

Title: MIRACLE
- Abraham *et al*., 2002,[6] 2001[84]
- Leon *et al*., 2005[86]
- Aranda *et al*., 2004[85]
- Woo *et al*., 2005[87]
- FDA report[88]

Country: USA and Canada

Setting: Multiple, 44 centres

Recruitment dates: November 1998–December 2000

Study design: Prospective, parallel RCT

Participants

Total number: 453 (control = 225, intervention = 228)

Inclusion criteria:
- ⩾18 years
- NYHA II or IV
- HF due to ischaemic or non-ischaemic cardiomyopathy for >1 month
- QRS interval ⩾130 ms
- LVEF ⩽35%
- LVEDD ⩾55 mm
- Optimal medical therapy

Exclusion criteria:
- 6-minute walk ⩾450 m
- Presence of pacemaker or ICD
- Indication for or contraindication to cardiac pacing
- Cardiac or cerebral ischaemic event ⩽3 months
- AF ⩽1 month
- Severe primary pulmonary disease
- Unstable angina, acute MI, coronary surgery ⩽3 months
- Life expectancy <6 months

Subgroups:
- Use of β-blockers
- Ischaemic vs non-ischaemic HF
- LVEF
- Left or right bundle block
- QRS duration
- Sex
- Age (identified *post-hoc*)

Patient baseline characteristics

At pre-randomisation and ⩽7 days pre-implantation

	Control	Intervention
N	225	228
Age mean (SD or range)[a] (years)	64.7 (11.2)	63.9 (10.7)
Male *n* (%)	68 (30)	68 (30)
Severity of heart failure		
Class I *n* (%)		
Class II *n* (%)		
Class III *n* (%)	91 (40)	90 (40)
Class IV *n* (%)		
Cardiac dyssynchrony (QRS)		
Mean (SD or range)[a]	165 (20)	167 (21)
LVEF mean (SD or range)[a]	21.6 (6.2)	21.8 (6.3)
Ischaemic HD *n* (%)	58 (26)	50 (22)
β-Blocker *n* (%)	55 (24)	62 (27)

Intervention

Intervention:
Optimal medical therapy
CRT-P
InSync Model 8040, Medtronic

Comparator:
Optimal medical therapy

CRT-P OFF:
VDI 35 (ventrical paced, A and V sensed, no response to sensing)
InSync Model 8040, Medtronic

Leads
LV: Attain 2187 or 2188
AV: not specified
RV: not specified

Concurrent treatment:
Medication for HF for both groups kept constant

Notes:
Only patients who were successfully implanted underwent randomisation

Outcome measures

Primary outcome measure:
- NYHA class
- MLHFQ QoL
- 6-minute walk

Secondary measures:
- All-cause mortality
- HF hospitalisations
- Exercise capacity – peak O_2 consumption, time on treadmill
- LVEF
- End diastolic diameter
- QRS duration
- Severity of mitral regurgitation
- Clinical response (composite – improved, worsened or unchanged)

continued

Spironolactone *n* (%)		
Atrial fibrillation *n* (%)		
ACE or angiotensin blocker *n* (%)	90 (40)	93 (41)
Left branch bundle block *n* (%)	313 (69)	
Right branch bundle block *n* (%)	43 (9)	

[a] Medians and IQRs reported

Method of assessing outcomes:
Mix of methods – event flagging, clinical assessment (exercise and heart function) and questionnaires (QoL) at baseline, implantation, discharge (⩽7 days postprocedure), 1, 3 and 6 months

Length of follow-up:
6 months

Results

	Control *n*	Control *N*	Intervention *n*	Intervention *N*	RR or HR (95% CI or *p*-value)
Effectiveness outcomes					
All-cause mortality					
At 6 months	16	225	12	228	HR 0.73 (0.34 to 1.54), $p = 0.40$
HF hospitalisations					
At 6 months (people)	34	225	18	228	HR 0.50 (0.28 to 0.88), $p = 0.02$
At 6 months (events)	50		25		
NYHA class					
At 6 months improved ⩾2 classes	12	196	34	211	
At 6 months improved 1 class	62	196	109	211	
No change	115	196	64	211	
Worsened	7	196	4	211	

	N	Mean	SD	*N*	Mean	SD	*p*-Value for between group difference
6-minute walk test (m)							
At baseline	225	291	101	228	305	85	
At 1 month change – median (95% CI) from graphic	196	+18 (+4 to +26)		212	+28 (+20 to +38)		$p = 0.005$
At 3 months change – median (95% CI) from graphic	196	+11 (–1 to +25)		212	+32 (+20 to +50)		$p = 0.003$
At 6 months change – median (95% CI)	198	+10 (0 to +25)		214	+39 (+26 to +54)		$p = 0.005$
Health-related QoL (MLHFQ)							
At baseline	225	59	21	228	59	20	
At 1 month change – median (95% CI) from graphic	192	–10 (–7 to –13)		211	–18 (–15 to –22)		$p < 0.001$
At 3 months change – median (95% CI) from graphic	192	–11 (–13 to –5)		211	–18 (–14 to –20)		$p < 0.001$
At 6 months change – median (95% CI)	193	–9 (–12 to –5)		213	–18 (–22 to –12)		$p = 0.001$
Peak 0_2 consumption (ml/kg/min)							
At baseline	225	13.7	3.8	228	14.0	3.5	
At 6 months change – median (95% CI)	145	+0.2 (–0.2 to +0.8)		158	+1.1 (+0.6 to +1.7)		$p = 0.009$
Total exercise time (s)							
At baseline	225	462	217	228	484	209	
At 6 months change – median (95% CI)	146	+19 (–1 to +47)		159	+81 (+62 to +119)		$p = 0.001$

Subgroups
Presented analyses stratified by subgroup with no mention of an interaction test (or equivalent). Therefore findings not presented

	Control *n*	Control *N*	Intervention *n*	Intervention *N*	RR or HR (95% CI)
Adverse outcomes					
Worsening HF					
HF requiring i.v. medication at 6 months	16	228	35	225	0.43 (0.27 to 0.77)
Others	"Frequency of AEs unrelated to device or to HF did not differ significantly between the two treatment groups". No figures reported				

continued

	Intervention *n*	*N*	Comments
Device-specific adverse outcomes			
Safety perioperative events (within 7 days of implant)			
Device or battery related	1	528	
Lead related	32	528	
Implant procedure or tools	23	528	
Heart function			
Infection			
Perforation or dissection	35[a]	571	Coronary-sinus (23) and cardiac vein or coronary sinus (12)
Heart block	6	571	Required permanent pacing
Death	1	571	Due to hypotension
Asystole	1	571	Revived by CPR and died 1 month later
Safety postoperative events (>8 days after implant)			
Device or battery related	13	528	
Lead related	45	528	
Implant procedure or tools	6	528	
Heart function			
Infection	7	528	All required explantation and four later re-implanted
Perforation or dissection			
Death (<30 days)	1	528	See above
Heart block			

Drop-outs (excluding death and need for transplant)	Control *n*	*N*	Intervention *n*	*N*	RR or HR (95% CI)
Reason: complication of device or simply missed 6-month follow up	6	225	1	228	
Unscheduled crossovers	10	225	0	228	

[a] Reported as 6/528 in Leon *et al*., (2005)[86]

Methodological comments	
Prospective recruitment?	Yes
Selection/randomisation:	Unknown
Method of randomisation:	Unknown
Block:	Yes
Stratification:	No
Concealment of allocation:	Yes, sealed envelope
Groups similar at baseline?	Yes
Eligibility criteria stated?	Yes
Appropriate?	Yes
Blinding:	Yes, both patients and outcome assessors blinded
Outcome measures:	Objective? Event outcome objective (classification by independent committee) and health-related QoL assessed using validated questionnaire
ITT: **If no, justified?**	Yes
Protocol violations specified:	Yes (crossovers before 6 months stated)
Follow-up/attrition:	All people accounted for? Yes Withdrawal specified? Yes Withdrawal reasons given? Yes Were intervention and control groups followed-up similarly? Yes Were both groups treated similarly apart from the intervention? Yes
Data analysis: **Are they appropriate?**	Statistical tests used: Yes, events compared with χ^2 and Cox's proportional hazards model and comparison of groups of continuous outcomes not stated

continued

How were missing data accounted for?	Analysis included last value carried forward analysis
Power calculation at design?	Yes on basis of 25% difference in NYHA, 13 point difference in MLHF and 50 m difference in 6-minute walk
Does it justify any subgroup analyses carried out?	*Post hoc* subgroup analyses reported based on analysis of covariance (ANCOVA) with no mention of an interaction test (or equivalent)
Are the conclusions supported by the results?	Yes
Was ethical approval given?	Yes
Generalisability:	47 patients not enrolled because the device was not successfully implanted (43), or they became medically unstable (2) or required pacing (2)
Conflict of interest:	Yes – trial supported by Medtronic and authors state conflicts
Inter-centre variability	Not discussed

General comments
- No significant interaction for primary outcome and subgroups (use of β-blockers; ischaemic vs non-ischaemic HF; left or right bundle block; QRS duration)
- Only patients who were successfully implanted underwent randomisation

Study

Title: MUSTIC-SR
- Cazeau *et al*., 2001[89]

Country: Europe

Setting: Multicentre, 15 centres

Recruitment dates: March 1998–March 1999

Study design: Crossover RCT

Participants
Total number: 67

Inclusion criteria:
- NYHA III
- HF for ⩾3 months due to idiopathic or ischaemic LVSD
- Optimal medical treatment
- ischaemic or non-ischaemic cardiomyopathy
- QRS interval ⩾150 ms
- LVEF ⩽35%
- LVEDD ⩾60 mm

Exclusion criteria:
- Hypertrophic or restrictive cardiomyopathy
- Suspected acute myocarditis
- Correctable vulvopathy
- ACS lasting ⩽3 months
- Revascularisation in previous 3 months or scheduled
- Treatment-resistant hypertension
- Obstructive lung disease
- An inability to walk
- Reduced life expectancy not associated with CVD
- An indication for an ICD
- Cardiac or cerebral ischaemic event within previous 3 months or had AF within previous month
- Life expectancy <1 year

Intervention
Intervention:
CRT-P ON
Chorum 7336 MSP, ELA Medical, France, and InSync Model 8040
Lead 2187 and 2188, Medtronic, USA

Comparator:
CRT-P OFF
With ventricular inhibited (inactive) pacing at a basic rate of 40 bpm

Concurrent treatment:
No modification to medication other than adjustment of the dose of diuretic allowed

Notes:
Only patients who were successfully implanted underwent randomisation

continued

Subgroups:
- Use of β-blockers
- Ischaemic vs non-ischaemic HF
- LVEF
- Left or right bundle block
- QRS duration
- Sex,
- Age (identified *post-hoc*)

Patient baseline characteristics
At baseline 4 weeks prior to implant

	All
N	67
Age mean (SD) (years)	63 (10)
Male *n* (%)	50 (75)
Severity of HF	
Class I *n* (%)	0
Class II *n* (%)	0
Class III *n* (%)	67 (100)
Class IV *n* (%)	0
Cardiac dyssynchrony (QRS)	
Mean (SD or range)[a]	
LVEF Mean (SD or range)[a]	23 (7)
Ischaemic HD *n* (%)	25 (37)
β-Blocker *n* (%)	19 (28)
Spironolactone *n* (%)	15 (22)
AF *n* (%)	
ACE or angiotension blocker *n* (%)	64 (96)
Left branch bundle block *n* (%)	58 (87)

[a] Reported in overall group; 23.7% (7)

Randomisation 2 weeks postimplant

	Control	Intervention
N	29	29
Age mean (SD) (years)	64 (8)	64 (11)
Male *n* (%)	24 (83)	19 (66)
Severity of HF		
Class I *n* (%)	0	0
Class II *n* (%)	0	0
Class III *n* (%)	29 (100)	29 (100)
Class IV *n* (%)	0	0
Cardiac dyssynchrony (QRS)		
Mean (SD or range)	172 (20)	172 (22)
LVEF mean (SD or range)		
Ischaemic HD *n* (%)		
Non-ischaemic HD *n* (%)		
β-Blocker *n* (%)		
Spironolactone *n* (%)		
Atrial fibrillation *n* (%)		
ACE or angiotension blocker *n* (%)		

Outcome measures
Primary outcome measure:
- Distance walked in 6 minutes

Secondary measures:
- HF hospitalisations
- Exercise capacity – peak 0_2 consumption
- LVEF
- Patient preference at end of crossover period

Method of assessing outcomes:
Clinical assessment (exercise test) and questionnaire (QoL) at baseline, randomisation, 3 and 6 months

Length of follow-up:
6 months

continued

Results[a]

	Control		Intervention		RR or HR (95% CI or *p*-value)
	n	***N***	***n***	***N***	
Effectiveness outcomes					
All-cause mortality					
At 3 months	0	29	1	29	
At 6 months	0	29	3	29	
HF hospitalisations					
At 3 months	9	29	3	29	
Sudden death					
At 6 months	0	29	2	29	
HF deaths					
At 6 months	0	29	2	29	

	N	**Mean**	**SD**	***N***	**Mean**	**SD**	***p*-Value for between group difference**
6-minute walk test (m)							
At baseline	29	346	111	29	354	110	$p = 0.82$
At 3 months	24	316.2	141.8	22	384.1	78.9	
Health-related QoL (MLHFQ)							
At baseline	29	46	25	29	48	19	$p = 0.66$
At 3 months	22	44	25	23	33.3	22	
Peak 0_2 consumption (ml/kg/min)							
At baseline	29	14.1	4.6	29	13.5	8.4	$p = 0.41$
At 3 months	20	14.8	3.9	18	15.9	5.8	

[a] No significant crossover or carry-forward effects noted by authors

	Control		Intervention		All		RR or HR (95% CI)
	n	***N***	***n***	***N***	***n***	***N***	
Adverse outcomes							
Worsening HF							
At 3 months (severe decompensation)	1	29	0	29			
At 6 months					2	48	
AF							
At 3 months							
At 6 months	1	29	0	29	1	48	
Perioperative							
Unsuccessful implants (all related to LV lead)			5	64			
Postoperative							
LV lead displacement			5	58			

	Control		Intervention		All		RR or HR (95% CI)
	n	***N***	***n***	***N***	***n***	***N***	
Drop-outs							
At 3 months							
Withdrawal of consent at randomisation					1	58	
Loss of pumping efficacy			2	29			
Sudden death			1	29			
At 6 months							
Sudden death			2	24			
Other non-HF or study related					1		
Unscheduled crossovers	1	29	0	29			

continued

Methodological comments	
Prospective recruitment?	Yes
Selection/randomisation:	Randomisation method not stated
Method of randomisation:	
Block:	Yes
Stratification:	Yes, by centre
Concealment of allocation:	Not stated
Groups similar at baseline?	Yes
Eligibility criteria stated?	Yes
Appropriate?	Yes
Blinding:	Yes, single-blind – patients blinded
Outcome measures:	Objective? Yes, standardised exercise test and health-related QoL assessed using validated questionnaire
ITT: **If no, justified?**	Yes
Protocol violations specified:	Yes (crossovers before 3 months stated)
Follow-up/attrition:	All people accounted for? Yes Withdrawal specified? Yes Withdrawal reasons given? Yes Were intervention and control groups followed-up similarly? Yes Were both groups treated similarly apart from the intervention? Yes
Data analysis: **Are they appropriate?**	Yes – events compared with χ^2 and comparison of groups of continuous outcomes using *t*- and Wilcoxon tests
How were missing data accounted for?	No imputation for missing cases undertaken
Power calculation at design?	Yes, on basis of 10% difference in 6-minute walk and 10% difference in MLHF
Does it justify any subgroup analyses carried out?	No subgroup analysis undertaken
Are the conclusions supported by the results?	Yes
Was ethical approval given?	Yes
Generalisability:	9 patients who met eligibility criteria were not randomised – 3 withdrew consent (2 developed unstable HF and 1 due to pre-existing indication for pacing), 5 due to failed response to CRT and 1 died during inactive phase
Conflict of interest:	Yes – trial supported by ELA, Medtronic and Swedish Heart Lung Association and Swedish MRC, and authors state conflicts
Inter-centre variability	Not discussed

General comments

- Only patients who were successfully implanted underwent randomisation
- Baseline measures taken 4 weeks prior to implant and at randomisation 2 weeks postimplant

Appendix 4
Excluded studies

Excluded studies are listed in *Table 78*, with reasons for exclusion.

TABLE 78 *Table of studies excluded at paper stage*

Study	Title	Reason for exclusion
Adamson *et al*., 2003	Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure	Inappropriate outcomes – heart rate variability
Fernandez *et al*., 2005	Antitachycardia pacing efficacy significantly improves with cardiac resynchronization therapy	Subgroup analysis of anti-tachycardia pacing – outside the scope of this TAR
Higgins *et al*., 2000	Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy	Subgroup analysis of tachycardia pacing – outside the scope of this TAR
Linde *et al*., 2002	Long-term benefits of biventricular pacing in congestive hear failure: results from the MUltisite STimulation In Cardiomyopathy (MUSTIC) study	Follow-up data from after the end of the crossover period
Varma *et al*., 2003	Atriobiventricular pacing improves exercise capacity in patients with heart failure and intraventricular conduction delay	Pre/postcrossover data cannot be separated out

Appendix 5

Clinical effectiveness charts and graphs

Figure 68 shows an assessment of the constancy of CRT treatment effect over time. Data were extracted from the individual Kaplan–Meier curves of the CARE-HF and COMPANION trials so that HRs for CRT-P compared with optimal medical therapy were obtained at various time points postimplant, i.e. 1, 3, 9, 12, 24 and 36 months. The HRs were then pooled at each of these separate time points (see box). The overall pooled HR at each time point is summarised in the Forest plot shown. There was evidence of no statistically significant heterogeneity ($Q = 5.292$ on four degrees of freedom, $p = 0.259$) across these five time points, indicating that treatment effects were relatively constant over time.

Pooled HRs of CRT-P survival time over 36 months are presented in *Figure 69* and Begg's funnel plots with 95% CIs are shown in *Figures 70–72*.

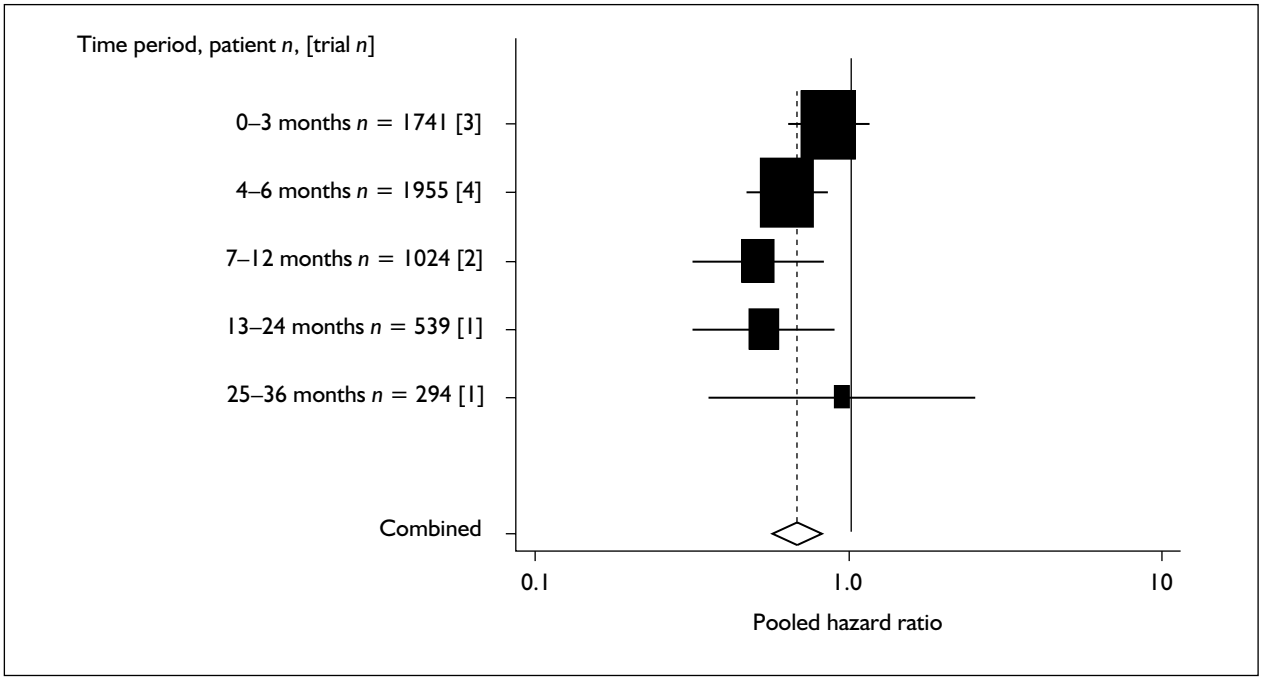


FIGURE 68 *Assessment of the constancy of CRT treatment effect over time*

```
meta lnHR se_lnHR if FU==3, eform gr(f) id( trial) cline xline(1) xlab(0.1,1> ,10)
Meta-analysis (exponential form)
      |  Pooled      95% CI      Asymptotic      No. of
Method  |  Est      Lower      Upper      z_value      p_value      studies
----------+-------------------------------------------------------------------
Fixed   |  0.862      0.640      1.159      -0.983      0.326      3
Random  |  0.862      0.640      1.159      -0.983      0.326

Test for heterogeneity: Q= 0.602 on 2 degrees of freedom (p= 0.740)
Moment-based estimate of between studies variance = 0.000

. meta lnHR se_lnHR if FU==6, eform gr(f) id( trial) cline xline(1)
Meta-analysis (exponential form)

      |  Pooled      95% CI      Asymptotic      No. of
Method  |  Est      Lower      Upper      z_value      p_value      studies
----------+-------------------------------------------------------------------
Fixed   |  0.636      0.472      0.855      -2.991      0.003      4
Random |  0.636      0.472      0.855      -2.991      0.003

Test for heterogeneity: Q= 2.925 on 3 degrees of freedom (p= 0.403)
Moment-based estimate of between studies variance = 0.000

. meta lnHR se_lnHR if FU==12, eform gr(f) id( trial) cline xline(1) xlab(0.1,> 1,10)

Meta-analysis (exponential form)

      |  Pooled      95% CI      Asymptotic      No. of
Method  |  Est      Lower      Upper      z_value      p_value      studies
----------+-------------------------------------------------------------------
Fixed   |  0.515      0.318      0.835      -2.694      0.007      2
Random |  0.517      0.307      0.870      -2.486      0.013

Test for heterogeneity: Q= 1.161 on 1 degrees of freedom (p= 0.281)
Moment-based estimate of between studies variance = 0.020

. meta lnHR se_lnHR if FU==24, eform gr(f) id( trial) cline xline(1) xlab(0.1,> 1,10)

Meta-analysis (exponential form)

      |  Pooled      95% CI      Asymptotic      No. of
Method  |  Est      Lower      Upper      z_value      p_value      studies

Fixed   |  0.536      0.318      0.905      -2.335      0.020      1
Random  |  0.536      0.318      0.905      -2.335      0.020

Test for heterogeneity: Q= 0.000 on 0 degrees of freedom (p=      .)
Moment-based estimate of between studies variance = 0.000

. meta lnHR se_lnHR if FU==36, eform gr(f) id( trial) cline xline(1) xlab(0.1,> 1,10)

Meta-analysis (exponential form)

      |  Pooled      95% CI      Asymptotic      No. of
Method  |  Est      Lower      Upper      z_value      p_value      studies
----------+-------------------------------------------------------------------
Fixed   |  0.952      0.356      2.546      -0.098      0.922      1
Random |  0.952      0.356      2.546      -0.098      0.922

Test for heterogeneity: Q= 0.000 on 0 degrees of freedom (p=      .)
Moment-based estimate of between studies variance = 0.000
```

FIGURE 69 *Pooled HRs of CRT-P survival time over 36 months*

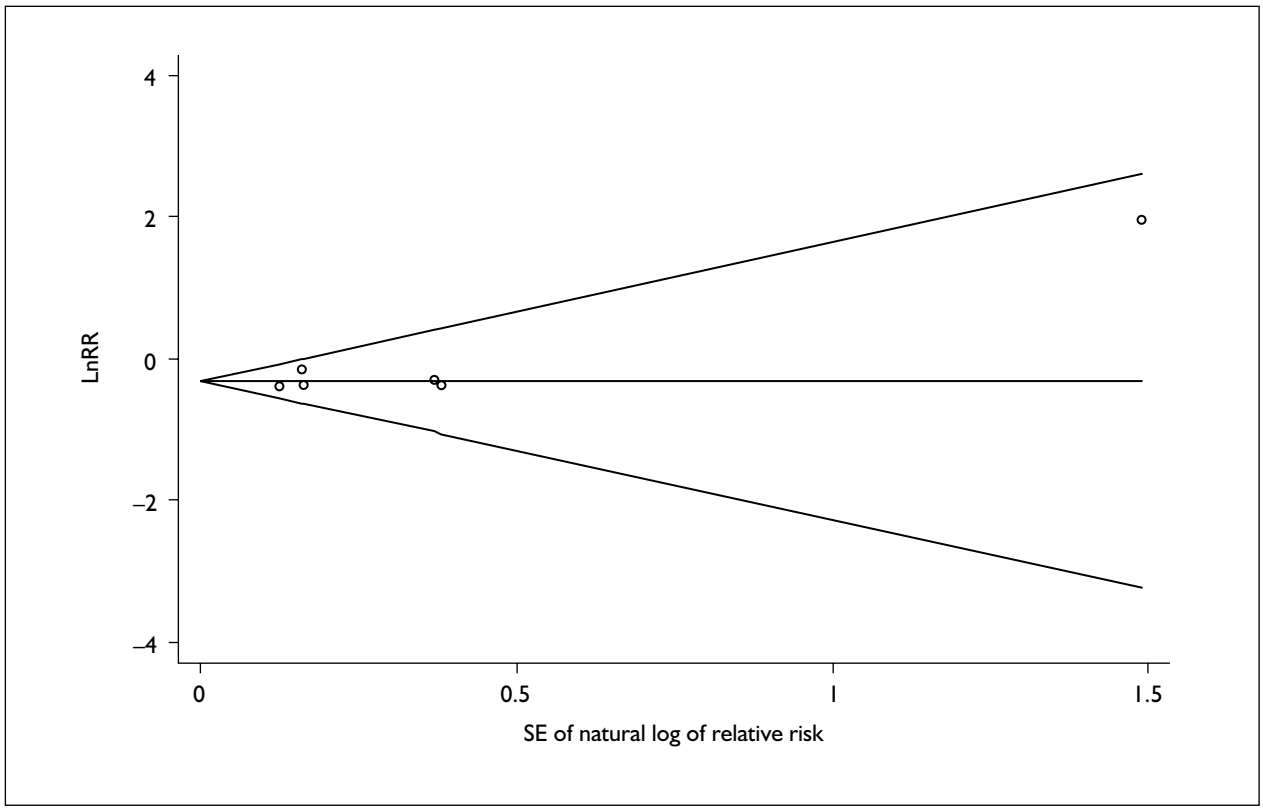


FIGURE 70 *Funnel plot for all-cause mortality*

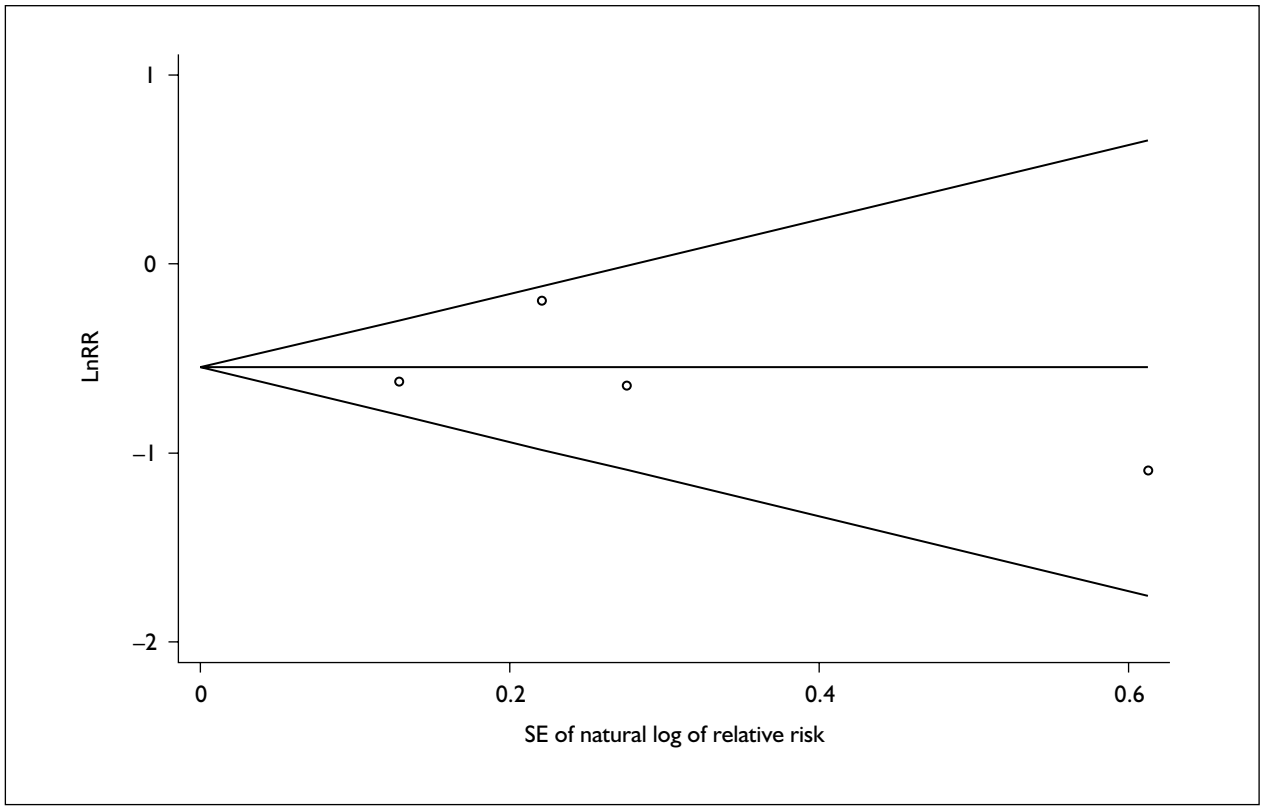


FIGURE 71 *Funnel plot for heart failure hospitalisation*

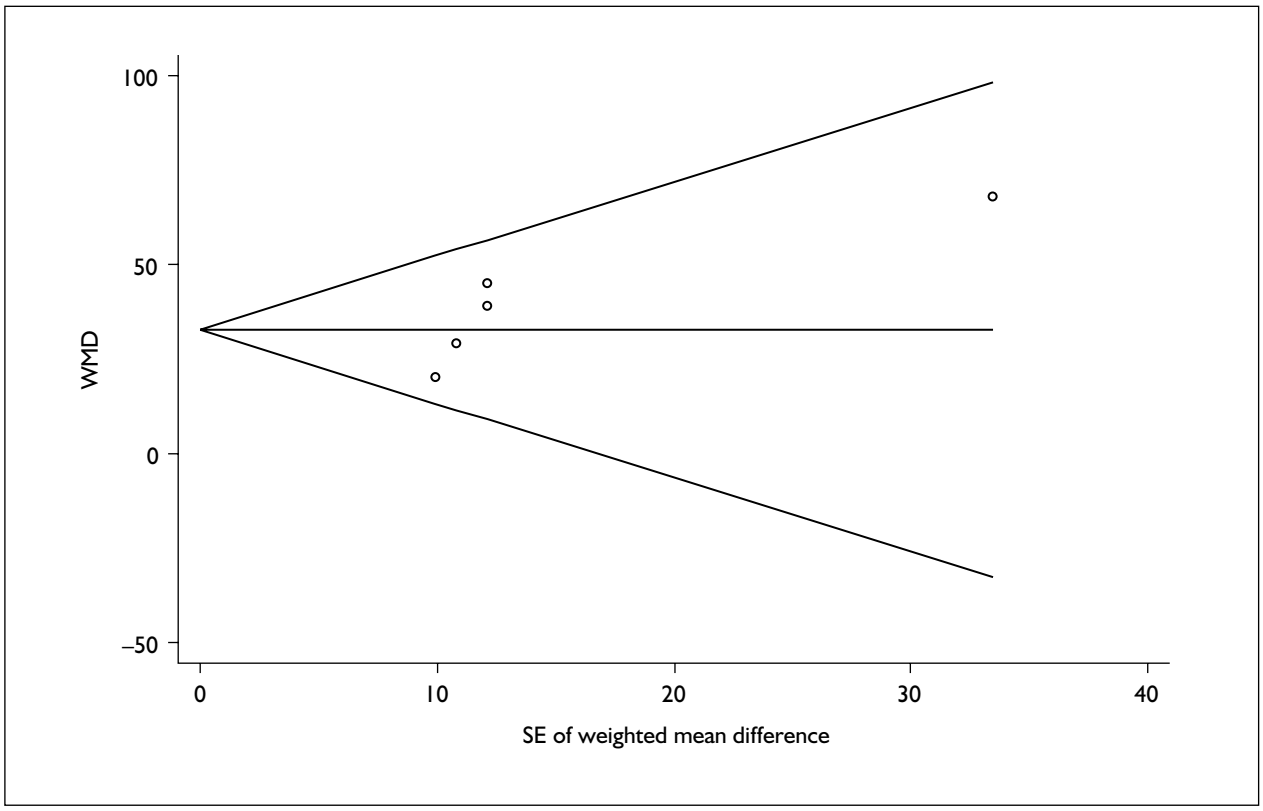


FIGURE 72 *Funnel plot for 6-minute walk test*

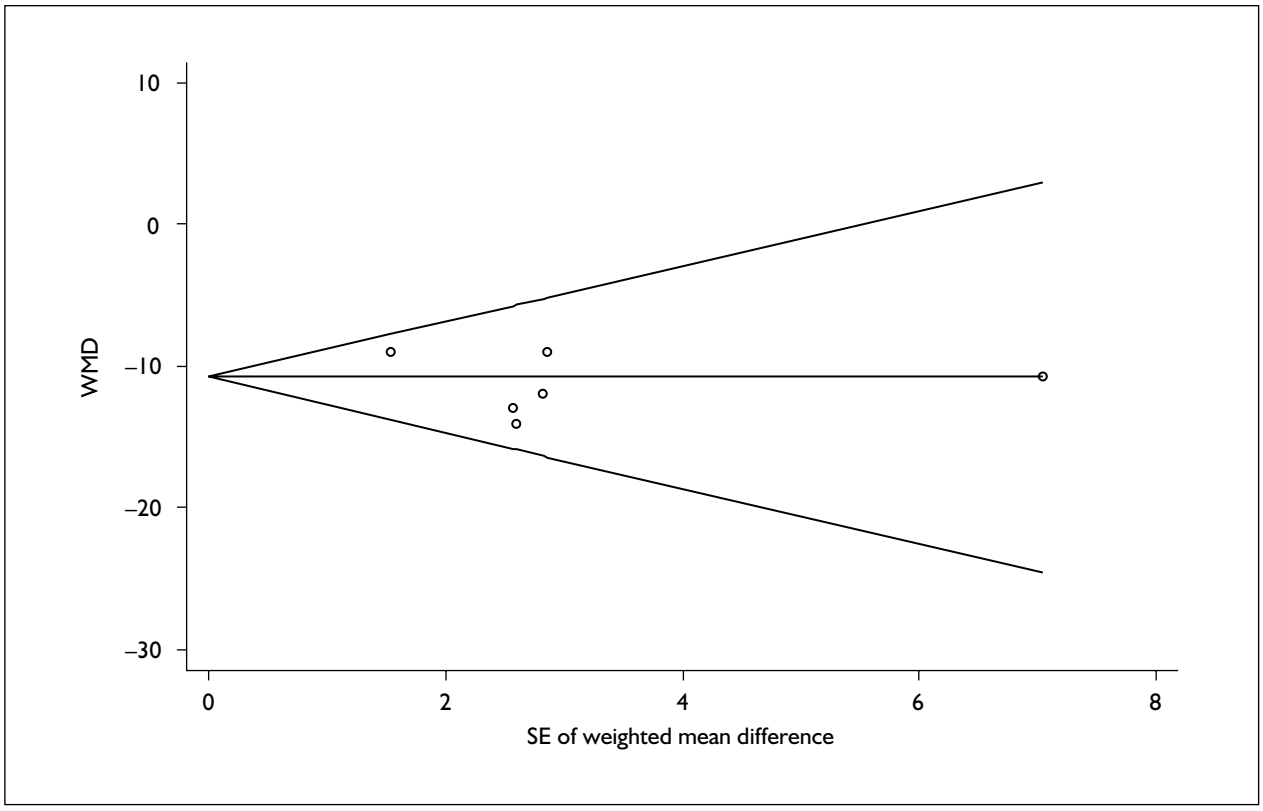


FIGURE 73 *Funnel plot for MLWHF*

Appendix 6

Economic evaluation tables

Relevant economic evaluation data are given in *Tables 79–81*.

TABLE 79 *Relevant published economic evaluations of CRT: study designs*

Study	Study type	Analysis type	Country and setting	Study population	Comparators	Perspective	Time horizon, discounting	Costs	Outcomes	Sensitivity analyses
Banz, 2005[111]	Decision model	CUA[a]	Germany	90% NYHA III 10% NYHA IV	CRT-P OPT	Payer and society	Model 5 years **but** base case analysis, only 1 year	*Events:* CRT procedure Hospitalisations (including intensive care unit days as % of above) Implant failure Heart transplant Various complications *Ongoing:* Drug treatment Outpatient follow-up	QALYs RR decrease in hospital days RR decrease in deaths	One-way Worst and best case
Nichol, 2004[112]	Decision model	CUA	USA	NYHA III	CRT-P OPT	Payer	Lifetime. Discounting at 3%	Hospitalisations (for CRT implant, lead failure, lead infection, battery replacement) Ambulatory visits Medications Laboratory tests	QALYs	One-way Selected two-way PSA and CEAC Structural SA Subgroup by NYHA class II and IV
Feldman, 2004[110] (abstract)	Trial + modelling extension of COMPANION trial	CEA	USA	As per COMPANION trial	CRT-P CRT-D OPT	Payer (Medicare)	5 years	Hospitalisations (for CRT implant, lead failure, lead infection, battery replacement) Ambulatory visits Medications Laboratory tests	Life-years	Not clear

continued

TABLE 79 *Relevant published economic evaluations of CRT: study designs (cont'd)*

Study	Study type	Analysis type	Country and setting	Study population	Comparators	Perspective	Time horizon, discounting	Costs	Outcomes	Sensitivity analyses
Fattore, 2005[113] (in Italian except abstract)	Decision model	CUA	Italy	90% NYHA III 10% NYHA IV (as Banz, 2005)	CRT-P OPT	NHS	1, 2 and 3 years Discounting at 3%	Hospitalisations (for CRT implant, lead infection, CRT revision)	QALYs	One-way and two-way
Feldman, 2005[109]	Trial	CUA	USA	As per COMPANION:	CRT-P CRT-D OPT	Payer (Medicare)	7 years	Hospitalisations (for CRT implant, lead failure, lead infection, battery replacement) Ambulatory visits Medications Laboratory tests	QALYs Life-years	One- and two-way PSA
Calvert, 2005[108]	Trial	CUA and CEA	Europe (12 countries) **but** UK costs	As per CARE-HF study: NYHA II and IV, LVEF <35%, LVEDD >30 mm, and QRS >120 ms	CRT-P OPT	Payer	As trial	Hospitalisations (for CRT implant, lead failure, lead infection, battery replacement, heart transplant, cardiac day case) Outpatient visits Primary care visits Residential and nursing home week Medication		One-way PSA and CEAC

CABG, coronary artery bypass graft; PTCA, angioplasty.
[a] "Preliminary" "illustrative" analysis.

TABLE 80 *Relevant model-based economic evaluations of CRT: model design and key assumptions*

Study	Model structure	Sources of probabilities	Sources of utilities	Sources of costs	Handling heterogeneity	Model validation
Banz, 2005[111]	Decision tree (split into 8 unequal time periods, over 5 years)	"Comprehensive review of published literature" Plus expert clinical opinion Abrahams *et al*., 2005	Value for each NYHA class, from Lewis, 2001	Germany-specific sources – but event rates from Abrahams, 2005 Some from expert data	NYHA class	Economic part of model, against BRESCIA study (Curnis, 2003)
McAlister, 2004[114]	Markov model, 9 states, cycle 1 month	Own meta-analysis and systematic review Death-with-complication rates – **assumed**	Own SG survey of $n = 90$(?) of general public, using expert-developed health state descriptions (HUI items)	Device manufacturers Kaul, 2003 and Owens, 1997 (for hospitalisations) Hospitalisation duration for complications – **assumed**	NYHA class (II, III and IV)	Peer review process of decision analysis
Nichol, 2004[112]	Markov model	Own systematic review (McAlister, 2004) Death-with-complication rates – **assumed**	Own SG survey of $n = 66$ of general public, using expert-developed health state descriptions (HUI items)	Device manufacturers Kaul, 2003 and Owens, 1997 (for hospitalisations) Hospitalisation duration for complications – **assumed**	NYHA class (III and IV)	Against mortality rate at 1 year
Fattore, 2005[113]	Decision tree or 4-cycle Markov model	Abrahams, 2005 and Nichol, 2004	Lewis, 2001	Italy-specific DRG costs, plus **expert assumption** for additional cost per implant failure	Not clear	Not clear

HUI, Health Utilities Index; SG, standard gamble.

TABLE 81 *Relevant published economic evaluations of CRT-P and CRT-D: results*

Study	From treatment	To treatment	Scenario	Incremental cost	Incremental QALYs	ICER (discounted)	ICER (not discounted)
Banz, 2005	OPT	CRT-P	Base case	€5,880	0.16 p.a.		€36,600/QALY
McAlister, 2004	OPT	CRT-P	Base case	~$32,900[a]	~0.35[a]	~$90,700/QALY[a]	
Nichol, 2004	OPT	CRT-P	Base case	~$30,000[a]	~0.28[a]	~$107,800/QALY[a]	
Fattore, 2005	OPT	CRT-P	Base case (1-year horizon)	€10,116	0.16	€63,225/QALY	
	OPT	CRT-P	Base case (2-year horizon)	€10,438	0.344	€30,343/QALY	
	OPT	CRT-P	Base case (3-year horizon)	€10,556	0.486	€21,720/QALY	
Feldman, 2005	OPT	CRT-P	Base case	$13,800[b]	0.71[b]		$19,600/QALY
	OPT	CRT-D	Base case	$36,200[b]	0.84[b]		$43,000/QALY
Calvert, 2005	OPT	CRT-P	Base case CUA	€4,316	0.22	€19,319/QALY	€18,756/QALY
					Incremental LYs		
Calvert, 2005	OPT	CRT-P	Base case CEA	€4,316	2.02	€43,596/LY	
Feldman, 2004 (abstract)	OPT	CRT-P	Base case: 5-year CEA	Not reported	Not reported	Not calculated "due to absence of a statistically significant mortality benefit"	
Feldman, 2004 (abstract)	OPT	CRT-D	Base case: 5-year CEA	$18,612	0.50	$36,870/LY	
Feldman, 2005	OPT	CRT-P	Base case	$13,800	0.49	$28,100/LY	
	OPT	CRT-D	Base case	$36,200	0.78	$46,700/LY	

LY, life-year.
[a] These are the reported median incremental cost, QALYs and cost per QALY (Table 15, p. 60 and Table 2, p. 347), which may or may not closely reflect the means.
[b] These are the undiscounted incremental costs and QALYs.

Appendix 7

Economic model plots

Weibull curve fitting in the economic model

The methods outlined below are those suggested by Collett[146] for the fitting of a standard Weibull curve and a Weibull proportional hazard model.

Assuming a random variable that follows a Weibull distribution defined by two parameters λ and γ, the corresponding survivor function is

$$S(t) = \exp(-\lambda t^{\gamma})$$

which can be equivalently written as

$$\ln\{-\ln[S(t)]\} = \ln\lambda + \gamma \ln t$$

If the assumption that the variable follows a Weibull distribution is valid, then a straight-line relationship between $\ln\{-\ln[S(t)]\}$ and $\ln t$ should be present (*Figure 74*).

Using Microsoft Excel to perform simple ordinary least-squares regression, estimates for lnλ and γ can be derived using $\ln t$ as the independent variable and $\ln\{-\ln[S(t)]\}$ as the dependent variable. The 95% CIs for both parameters are generated during the process. A similar plot was produced to test the Weibull assumption for death from heart failure in patients receiving OPT.

To test whether a Weibull proportional hazard model is suitable for use in comparing two patient groups, the following method is used. First, the above method must be applied to both groups to obtain log cumulative hazard plots for both, and second, these plots must be analysed to see if the lines produced are both approximately straight and parallel. *Figure 75* shows the log cumulative hazard plot for death from worsening HF in people in both the OPT and CRT-P arms of the CARE-HF trial.

Both lines are reasonably straight, suggesting that the assumption that both follow a Weibull distribution is valid. The two lines appear to be approximately parallel, suggesting that the assumption of a proportional hazard between the

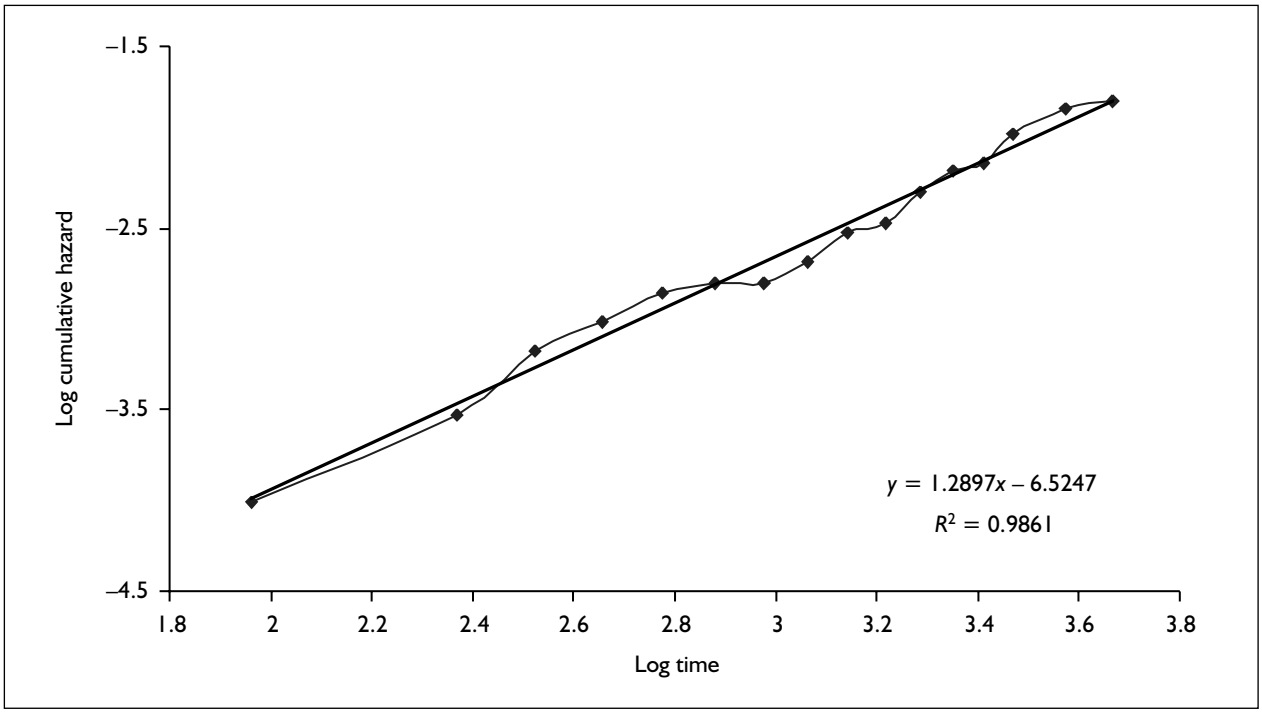


FIGURE 74 *Log cumulative hazard plot used in the fitting of a survival curve to the CARE-HF Kaplan–Meier curve for SCD in people receiving OPT*

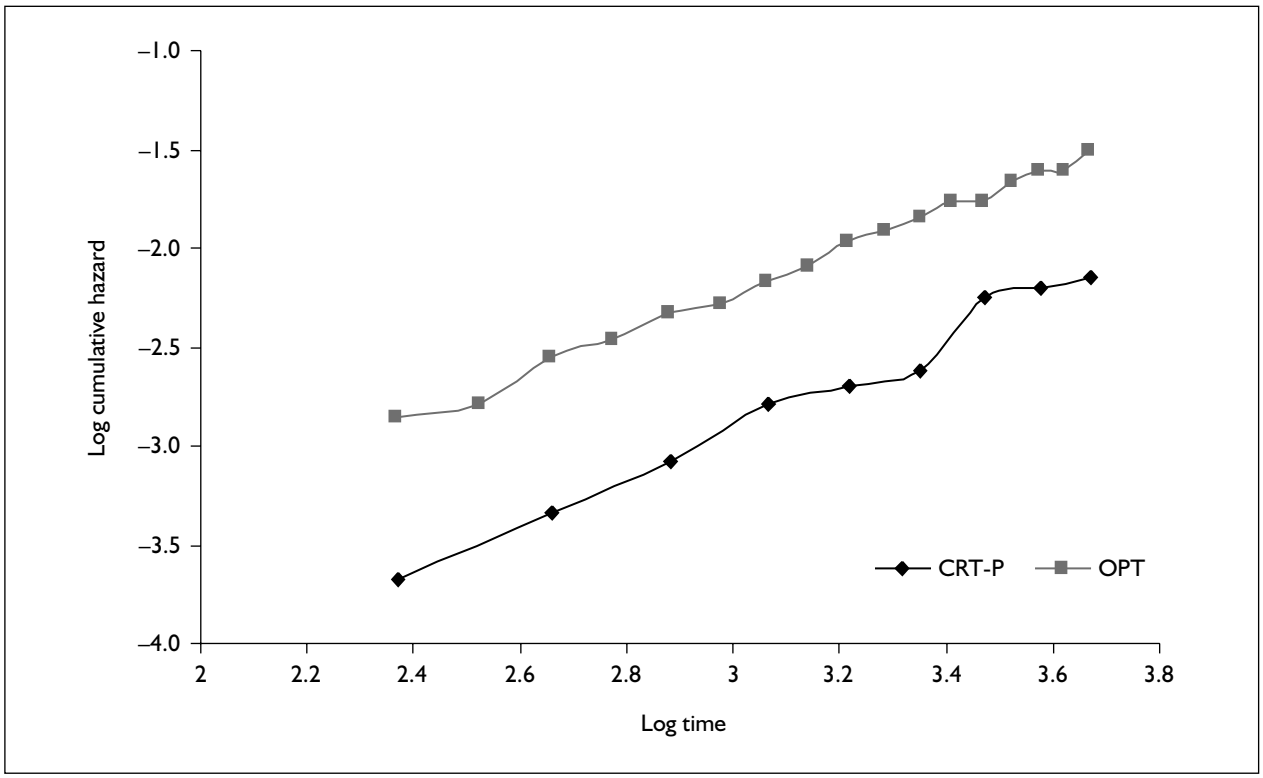


FIGURE 75 *Log cumulative hazard plot for death from worsening HF in people in both OPT and CRT-P arms of the CARE-HF trial*

two groups is also valid. A similar analysis for data presented in the COMPANION trial[76] showed that a Weibull proportional hazard model was also suitable for modelling survival in people in the CRT-D group compared with the OPT group.

Following on with the method described by Collett,[146] the survival curves in the CRT-P and CRT-D groups are defined using the equation $S(t) = \exp[-(HR\lambda)t^{\gamma}]$, where *HR* refers to the required HRs derived as part of the systematic review. *Tables 82* and *83* summarise the parameters used to fit survival curves for the OPT, CRT-P, CRT-D and ICD submodels.

Probability trees for the PenTAG economic model

The method described in this Appendix shows how the transition probabilities are generated in the OPT submodel. This method can also be used to derive the transition probabilities in the other three submodels.

Each health state in the PenTAG model has a corresponding probability tree used to derive a list of feasible transition probabilities. *Figures 76–81* show a selection of probability trees for people in the CRT-P submodel as presented in the section 'Threshold analysis' (p. 85).

TABLE 82 *Parameters used to fit Weibull curves for SCD in all submodels*

Device	HR	Parameter	Value	95% CI
None (OPT)	1 (reference case)	λ	0.0015	0.0011 to 0.0019
		γ	1.29	1.20 to 1.38
CRT-P	0.81	λ	0.0012	0.0009 to 0.0016
		γ	1.29	1.20 to 1.38
CRT-D	0.44	λ	0.0007	0.0005 to 0.0008
		γ	1.29	1.20 to 1.38
ICD	0.37	λ	0.0005	0.0004 to 0.0007
		γ	1.29	1.20 to 1.38

TABLE 83 *Parameters used to fit Weibull curves for death from worsening HF in all submodels*

Device	HR	Parameter	Value	95% CI
None (OPT)	1 (reference case)	λ	0.0028	0.0022 to 0.0034
		γ	1.21	1.14 to 1.28
CRT-P	0.65	λ	0.0018	0.0014 to 0.0022
		γ	1.21	1.14 to 1.28
CRT-D	0.65	λ	0.0018	0.0014 to 0.0022
		γ	1.21	1.14 to 1.28
ICD	0.95	λ	0.0026	0.0021 to 0.0032
		γ	1.21	1.14 to 1.28

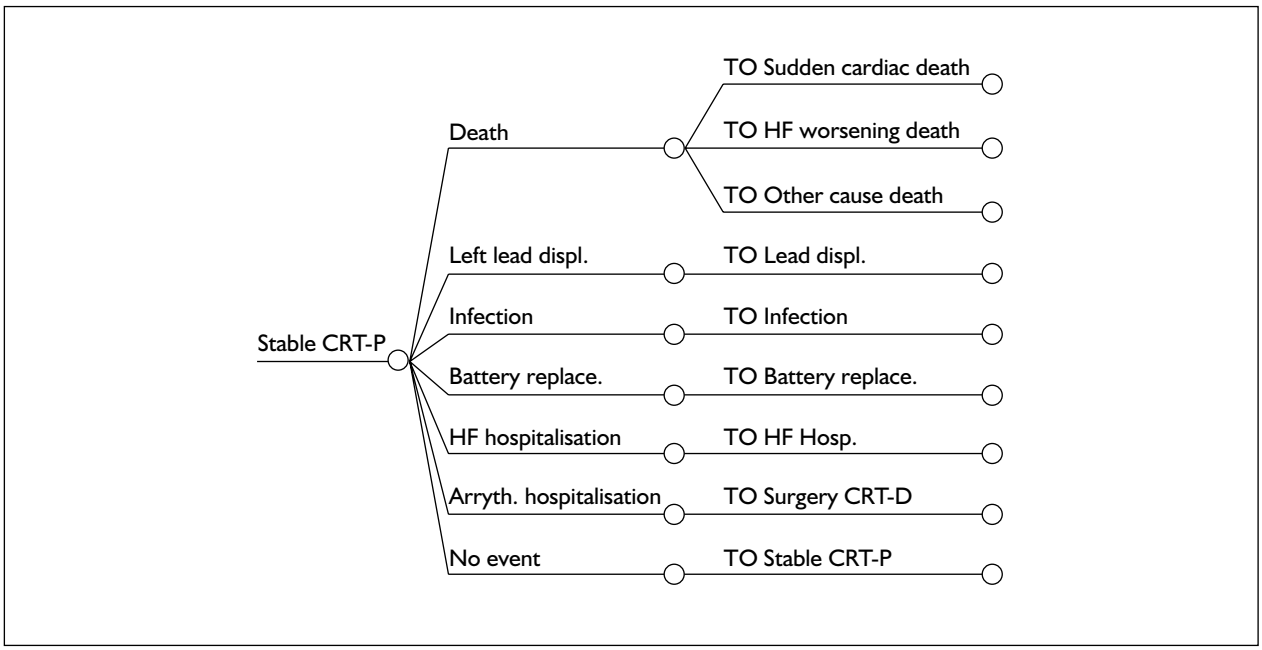


FIGURE 76 *Probability tree used to derive transition probabilities from the CRT-P stable state*

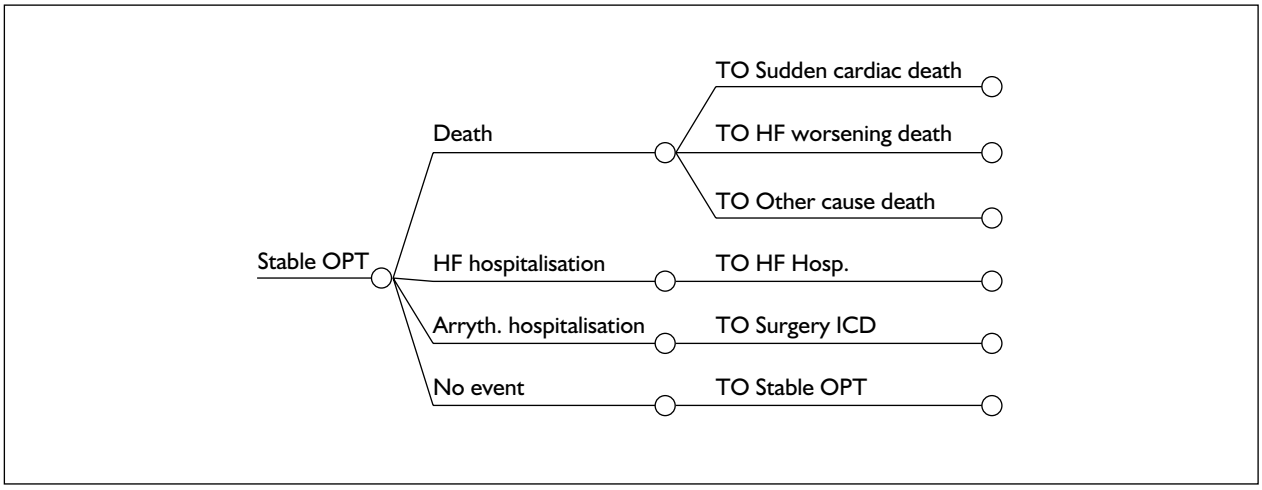


FIGURE 77 *Probability tree used to derive transition probabilities from the OPT stable state*

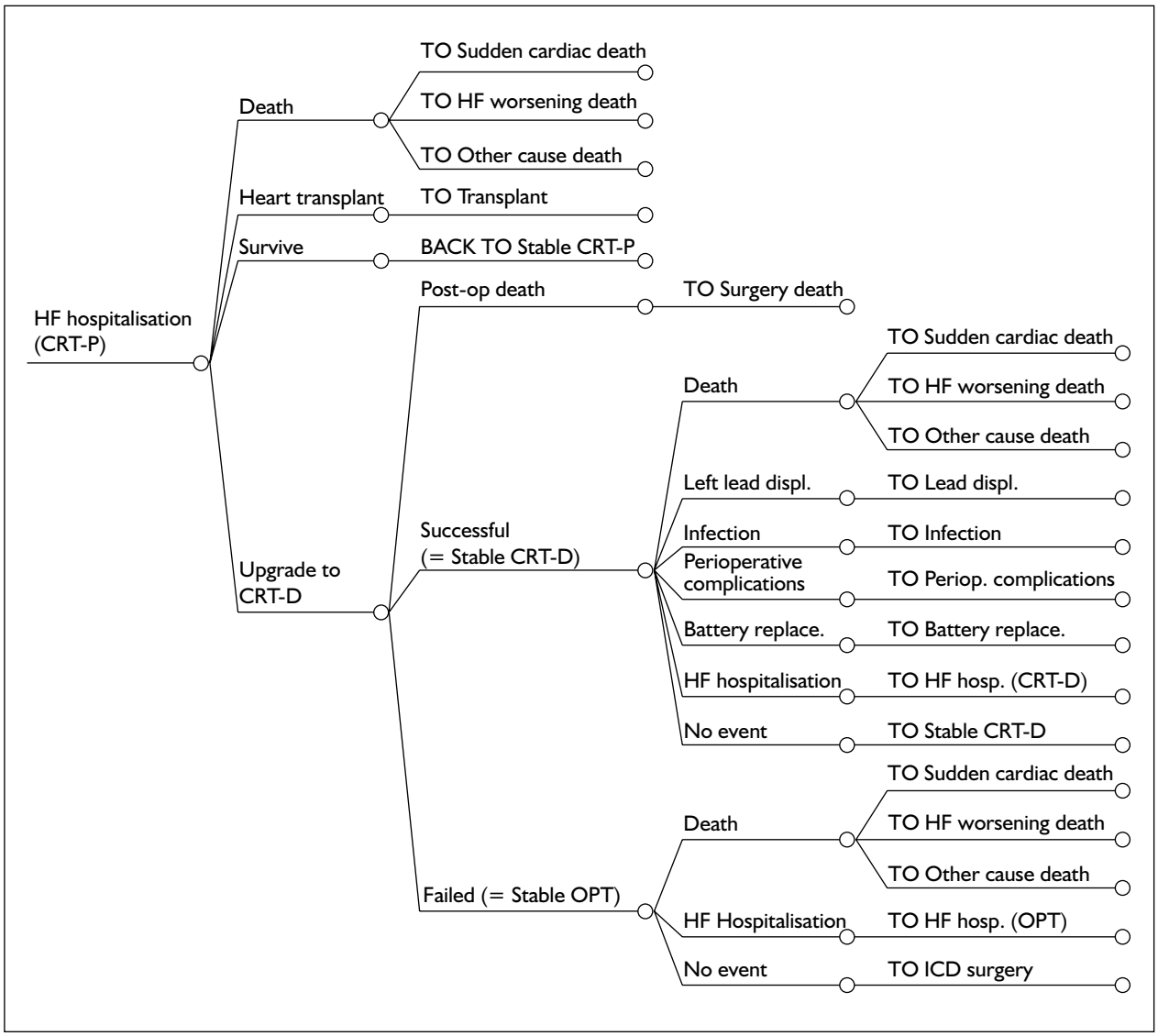


FIGURE 78 *Probability tree used to derive transition probabilities from the CRT-P HF hospitalisation state*

As reported in the main body of the TAR, transition probabilities are derived from the individual event probabilities by a process of multiplication. For each potential pathway between two states, the transition probability is derived by multiplying the individual event probabilities. Where there are multiple ways to arrive at a state from a given state, then the overall transition probability is the sum of all the individual paths.

For example, people can move from the lead displacement with CRT-P (PLD) state to the sudden cardiac death (SCD) state along two pathways:

- *P*(successful operation) × *P*(sudden cardiac death with CRT-P)

or

- *P*(unsuccessful operation) × *P*(sudden cardiac death with OPT)

Therefore, the overall transition probability used in the model will be

$$P(\text{PLD} \rightarrow \text{SCD}) = P(\text{successful operation}) \times P(\text{sudden cardiac death CRT-P}) + P(\text{unsuccessful operation}) \times P(\text{sudden cardiac death with OPT})$$

Ranges and distributions used in the PSA are given in *Table 84*.

Incremental analysis for non-reference case scenarios with justification

Table 86 shows a higher base case ICER than produced with the default time horizon set to

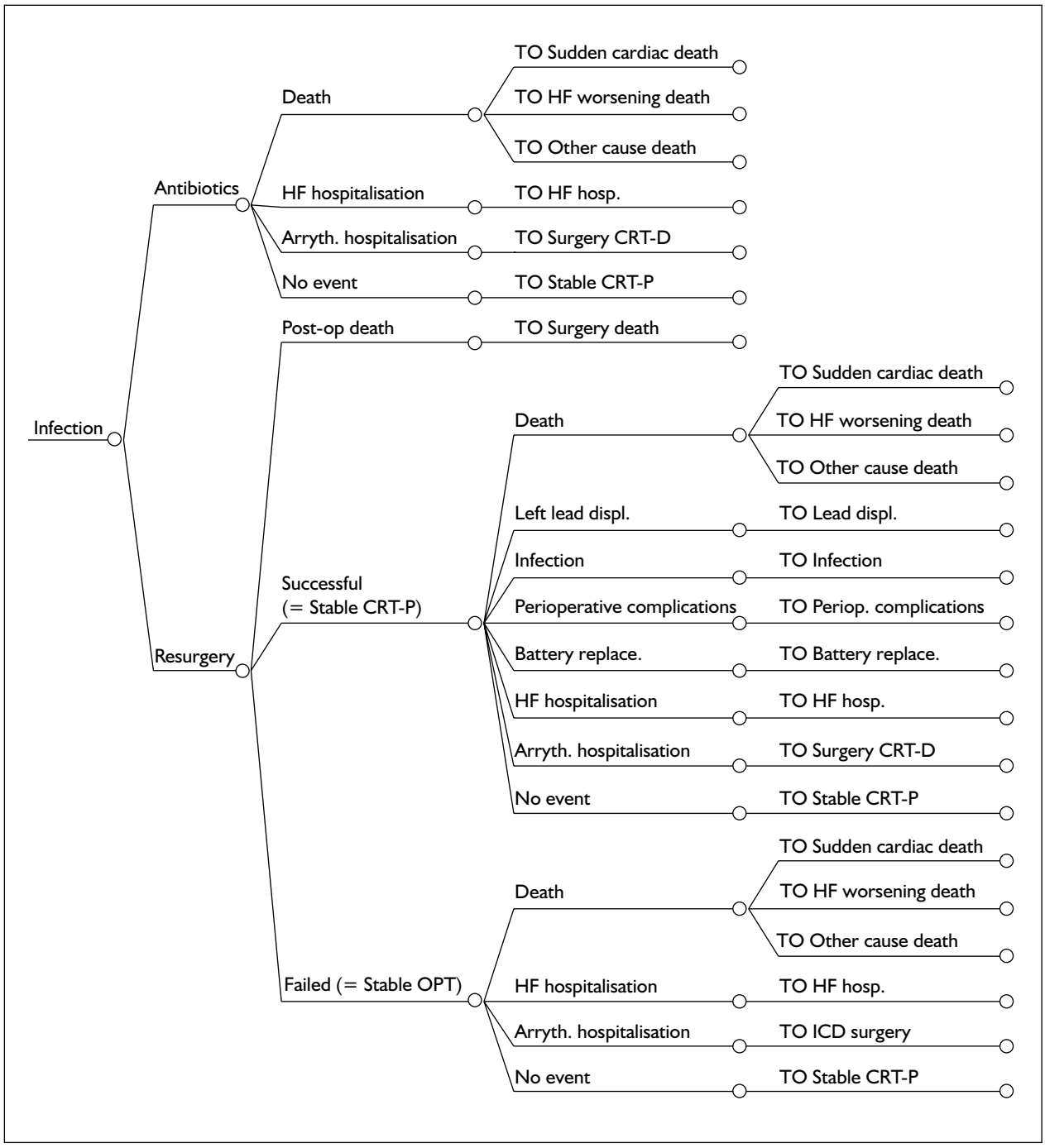


FIGURE 79 *Probability tree used to derive transition probabilities from the CRT-P lead displacement state*

cohort death, and a marked lack of age-related heterogeneity in both the incremental values and headline ICERS.

In contrast to what happened to the cost-effectiveness of a CRT-P device, shortening the time horizon increases the ICER dramatically. This is almost certainly due to the fact that in the first 5 years persons have not been given enough time to accrue enough QALYs to overcome the cost of the initial operation. If the very old are excluded from the analysis, the ICER decreases with starting age.

Both types of CRT devices accrue QALYs relatively quickly when compared with OPT (*Tables 85* and *86* show the QALY gains over the first 5 years of the model). *Table 87* shows that when compared to each other directly, the incremental difference for CRT-D as opposed to CRT-P is very slight. This is

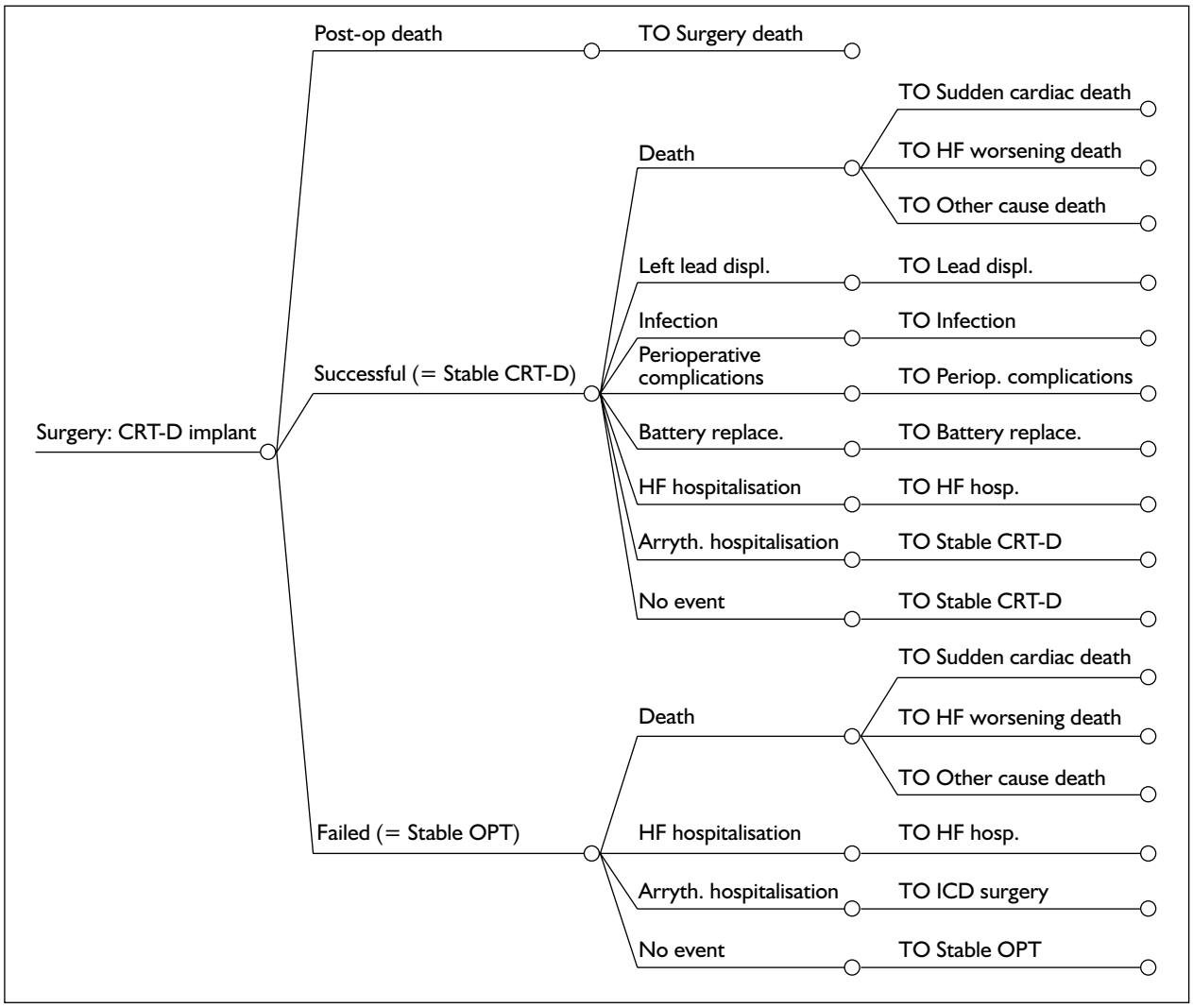


FIGURE 80 *Probability tree used to derive transition probabilities from the CRT-D surgery upgrade state*

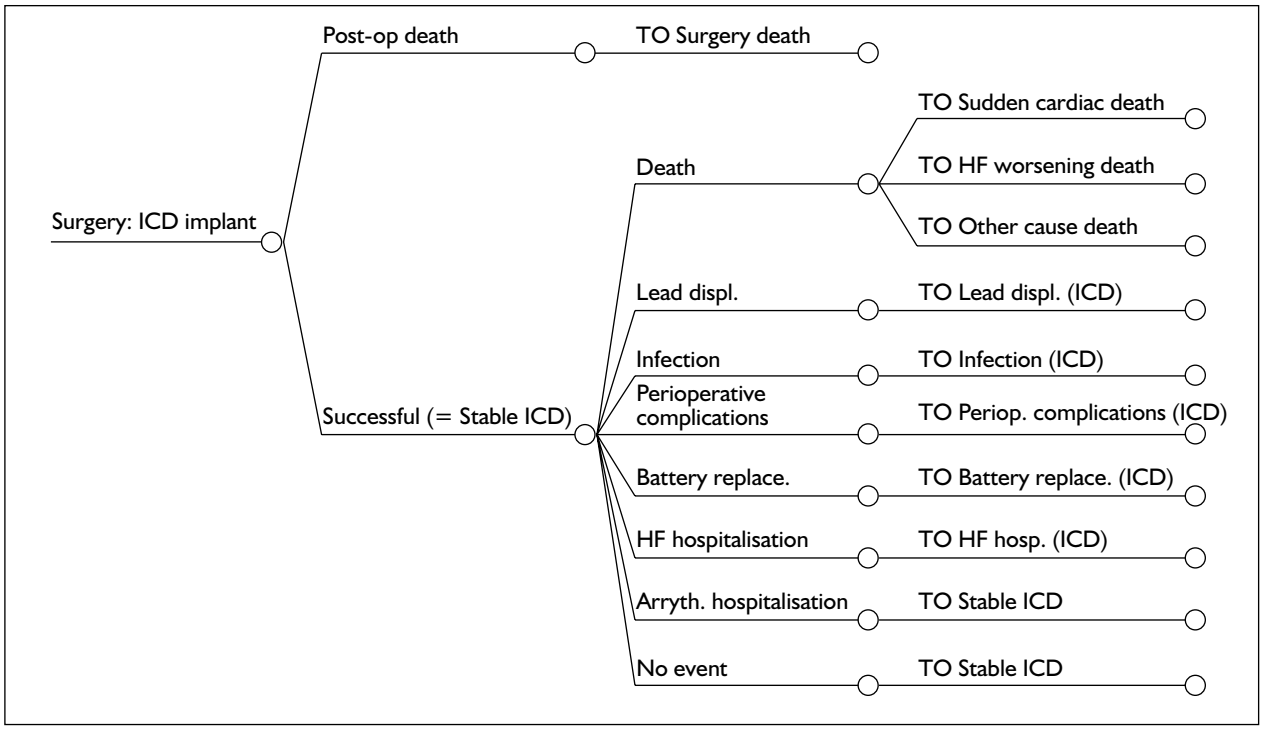


FIGURE 81 *Probability tree used to derive transition probabilities from the ICD surgery upgrade state*

TABLE 84 *Ranges and distributions used in the probabilistic sensitivity analysis*

Parameter	Available range data	Source	Type of data	Distribution
Utilities				
Value associated with hospitalisation due to HF	(0.48, 0.8)	McAlister *et al.*. 2004[114]	95% CI	Beta
Value associated with NYHA I	(0.912, 0.960)	Kirsch and McGuire, 2000[127]	95% CI	Beta
Value associated with NYHA II	(0.722, 0.842)	Kirsch and McGuire, 2000[127]	95% CI	Beta
Value associated with NYHA III	(0.591, 0.631)	Calvert *et al*., 2005[128]	Central estimate ± 0.02 (assumed 95% CI)	Beta
Value associated with NYHA IV	(0.421, 0.461)	Calvert *et al*., 2005[128]	Central estimate ± 0.02 (assumed 95% CI)	Beta
Proportion of patients in NYHA III at baseline	None	SE assumed to be 1/10th mean value	Assumption	Beta
Proportion of patients in NYHA IV at baseline	None	1-proportion of patients in class III	Assumption	NA
Proportion of patients on OPT class I or II after 90 days	None	SE assumed to be 1/10th mean value	Assumption	Beta
Proportion of patients with CRT device class I or II after 90 days	None	SE assumed to be 1/10th mean value	Assumption	Beta
NYHA distribution of patients on OPT at 180 days	NA	Baseline distribution taken from Curnis *et al*., 2003[147]	NA	Dirichlet
NYHA distribution of patients with CRT device at 180 days	NA	Baseline distribution taken from Curnis *et al*., 2003[147]	NA	Dirichlet
Scaled reduction applied to baseline utility for those experiencing postsurgical complications	[0, 0.1]	Assumption	Assumption	Uniform
Scaled reduction applied to baseline utility for those experiencing infections	[Value generated for surgical complications, 0.15]	Assumption	Assumption	Constrained uniform
Proportion of month spent in hospital when hospitalised for worsening HF	[20%, 30%]	Assumption	Assumption	Beta
Costs				
CRT-P implant surgery	(£4,997, £5,197)	NHS PASA	IQR	Log-normal
CRT-D implant surgery	(£17,197, £17,389)	NHS PASA	IQR	Log-normal
ICD implant surgery	(£11,558, £11,658)	NHS PASA	IQR	Log-normal
CRT-P elective battery replacement	(£3,281, £3,381)	NHS PASA	IQR	Log-normal
CRT-D elective battery replacement	(£14,985, £15,085)	NHS PASA	IQR	Log-normal
ICD elective battery replacement	(£11,488, £11,588)	NHS PASA	IQR	Log-normal
CRT-P infection	(£6,145, £10,475)	NHS PASA	IQR	Log-normal
CRT-D infection	(£18,959, £22,937)	NHS PASA	IQR	Log-normal
ICD infection	(£13,328, £17,026)	NHS PASA	IQR	Log-normal
CRT-P lead displacement	(£1,547, £1,747)	NHS PASA	IQR	Log-normal

continued

TABLE 84 *Ranges and distributions used in the probabilistic sensitivity analysis (cont'd)*

Parameter	Available range data	Source	Type of data	Distribution
CRT-D lead displacement	(£1,547, £1,747)	NHS PASA	IQR	Log-normal
ICD lead displacement	(£819, £919)	NHS PASA	IQR	Log-normal
Heart transplant	(14,525, £40,150)	NHS PASA	IQR	Log-normal
Non-elective hospitalisation due to worsening HF	(£932, £2,579)	NHS PASA	IQR	Log-normal
Non-elective hospitalisation for arrhythmia	(£443, £1,656)	NHS PASA	IQR	Log-normal
Outpatient cardiology follow-up (6 monthly)	(£73, £115)	NHS NSRC, 2005[56]	IQR	Log-normal
Drugs cost (per cycle) NYHA I	(£3, £12)	Expert opinion (drug types and doses) and BNF51[118]	IQR	Log-normal
Drugs cost (per cycle) NYHA II	(£3, £12)	Expert opinion (drug types and doses) and BNF51[118]	IQR	Log-normal
Drugs cost (per cycle) NYHA III	(£7, £18)	Expert opinion (drug types and doses) and BNF51[118]	IQR	Log-normal
Drugs cost (per cycle) NYHA IV	(£9, £22)	Expert opinion (drug types and doses) and BNF51[118]	IQR	Log-normal
Mortality				
Probability of perioperative death	None relevant	Mean and variance assumed to be same as trial point estimate	Counts of events observed in trials	Poisson
Cycle-dependent SCD in patients on OPT	(–6.79, –6.26) (1.20, 1.38)	Derived from data presented in the CARE-HF extension study	95% CIs for log λ and γ parameters used in calculation of each probability	Bivariate normal
Cycle-dependent death as a result of worsening HF in patients on OPT	(–6.12, –5.69) (1.14, 1.28)	Derived from data presented in the CARE-HF extension study	95% CIs for log λ and γ parameters used in calculation of each probability	Bivariate normal
Risk modifier applied to all forms of death in patients <64 years old	(0.54, 0.72)	Derived from data presented in Shahar *et al*., 2004[123]	95% CI	Log-normal
Risk modifier applied to all forms of death in patients >75 years old	(1.4, 1.42)	Derived from data presented in Shahar *et al*., 2004[123]	95% CI	Log-normal
Hospitalisation due to HF in patients with a CRT device (compared with those on OPT)	(0.45, 0.94)	PenTAG systematic review, Chapter 3	95% CI	Log-normal
Risk modifier for sudden death in patients with a CRT-P device (compared with those on OPT)	(0.45, 1.18)	PenTAG systematic review, Chapter 3	95% CI	Log-normal
Risk modifier for sudden death in patients with a CRT-D device (compared with those on OPT)	(0.23, 0.86)	PenTAG systematic review, Chapter 3	95% CI	Log-normal
Risk modifier for sudden death in patients with an ICD device (compared with those on OPT)	(0.27, 0.5)	Ezekowitz *et al*., 2003[125]	95% CI	Log-normal

continued

TABLE 84 *Ranges and distributions used in the probabilistic sensitivity analysis (cont'd)*

Parameter	Available range data	Source	Type of data	Distribution
Risk modifier for death from worsening HF in patients with a CRT device (compared with those on OPT)	(0.46, 0.98)	PenTAG systematic review, Chapter 3	95% CI	Log-normal
Risk modifier for death from worsening HF in patients with an ICD device (compared with those on OPT)	(0.74, 1.21)	Lee *et al*., 2004[28]	95% CI	Log-normal
Risk modifier for mortality postheart transplant	None	SE assumed to be 1/10th log mean value	Assumption	Log-normal
Event probabilities				
Probability of hospitalisation due to worsening HF in patients on OPT	None	Mean and variance assumed to be same as trial point estimate	Counts of events observed in trials. Number of observed events relatively large	Normal approximation to Poisson
Probability of hospitalisation due to worsening HF in patients with a CRT device	None	Derived from probability for patients on OPT and risk modifier	Assumption	Derived from parameters drawn from Poisson approximation and log-normal distributions
Probability of perioperative complications postdevice implant	None	Mean and variance assumed to be same as trial point estimate	Counts of events observed in trials. Number of observed events relatively large	Normal approximation to Poisson
Probability patient dies following any form of operation in a particular cycle	None	Mean and variance assumed to be same as trial point estimate	Counts of events observed in trials	Poisson
Probability patient with a CRT device experiences an infection	None	Mean and variance assumed to be same as trial point estimate	Counts of events observed in trials	Poisson
Patient with a CRT device experiences a lead displacement	None	SE assumed to be 1/10th mean value	Assumption	Beta
Patient experiences an arrhythmic event with OPT or CRT-P	None	Mean and variance assumed to be same as point estimates in trials	Counts of events observed in trials. Number of observed events relatively large	Normal approximation to Poisson
Patient receives a defibrillator upgrade after being hospitalised due to HF	None	Mean and variance assumed to be same as point estimates in trials	Counts of events observed in trials. Number of observed events relatively large	Normal approximation to Poisson
Transplant post-HF hospitalisation	None	SE assumed to be 1/10th log mean value	Assumption	Beta
Structural parameters				
CRT-P pulse generator replacement	(5, 8)	Industry personal communication Expert opinion	Assumed 95% CI	Log-normal

continued

TABLE 84 *Ranges and distributions used in the probabilistic sensitivity analysis (cont'd)*

Parameter	Available range data	Source	Type of data	Distribution
CRT-P pulse generator replacement	[4, 7]	Industry personal communication Expert opinion	Assumed 95% CI	Log-normal
ICD pulse generator replacement	[4, 8]	Expert opinion	95% CI	Log-normal
Starting ages of cohort	Population-based statistics	Office of National Statistics[23]	Stratification of events by age group	User-defined discrete distribution defined in Chapter 4

SE, standard error.

TABLE 85 *Discounted base case cost-effectiveness results per person for CRT-P compared with OPT based on shortened time horizon (5 years)*

Start age (years)	OPT costs (£)	OPT QALYs	CRT-P costs (£)	CRT-P QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
30	6,535	2.73	15,569	3.07	9,034	0.34	26,322
40	6,529	2.72	15,559	3.07	9,030	0.34	26,350
50	6,513	2.72	15,532	3.06	9,019	0.34	26,398
60	6,471	2.70	15,462	3.04	8,991	0.34	26,524
70	5,773	2.39	14,553	2.76	8,780	0.37	23,780
80	4,983	2.04	13,411	2.41	8,428	0.37	22,821
90	4,323	1.74	12,233	2.05	7,910	0.30	26,136
Mixed	**5,394**	**2.22**	**13,950**	**2.57**	**8,556**	**0.35**	**24,256**

TABLE 86 *Discounted base case cost-effectiveness results per person for CRT-D compared with OPT based on shortened time horizon (5 years)*

Start age (years)	OPT costs (£)	OPT QALYs	CRT-D costs (£)	CRT-D QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
30	6,535	2.73	23,132	3.15	16,597	0.42	39,610
40	6,529	2.72	23,126	3.14	16,597	0.42	39,656
50	6,513	2.72	23,111	3.13	16,598	0.42	39,785
60	6,471	2.70	23,070	3.11	16,599	0.41	40,117
70	5,773	2.39	22,610	2.86	16,837	0.47	35,874
80	4,983	2.04	22,000	2.52	17,018	0.48	35,271
90	4,323	1.74	21,305	2.14	16,982	0.39	43,406
Mixed	**5,394**	**2.22**	**22,273**	**2.67**	**16,879**	**0.45**	**37,443**

TABLE 87 *Discounted base case cost-effectiveness results per person for CRT-D compared with CRT-P based on shortened time horizon (5 years)*

Start age (years)	CRT-P costs (£)	CRT-P QALYs	CRT-D costs (£)	CRT-D QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
30	15,569	3.07	23,132	3.15	7,563	0.08	99,599
40	15,559	3.07	23,126	3.14	7,567	0.08	99,792
50	15,532	3.06	23,111	3.13	7,579	0.08	100,311
60	15,462	3.04	23,070	3.11	7,609	0.07	101,719
70	14,553	2.76	22,610	2.86	8,057	0.10	80,474
80	13,411	2.41	22,000	2.52	8,589	0.11	75,911
90	12,233	2.05	21,305	2.14	9,072	0.09	102,398
Mixed	**13,950**	**2.57**	**22,273**	**2.67**	**8,323**	**0.10**	**84,891**

primarily due to the utilities being used for states in both the CRT-P and CRT-D arms of the model being identical.

Undiscounted values: model outputs

It is standard practice for the presentation of the results of economic evaluations to give the results without, as well as with, discounting of costs and benefits. The undiscounted results for the three pairwise technology comparisons are shown in *Tables 88–90*. As expected, both the costs and QALYs are consistently higher. However, for all three comparisons, the ICERs are lower. The cost per QALY gained by moving from CRT-D to CRT-P is about £8000 or 11% lower when costs and QALYs are not discounted. The change in the ICER is smaller for the other two comparisons.

TABLE 88 *Undiscounted base case cost-effectiveness results per person for CRT-P compared with OPT (lifetime time horizon), by age and mixed age cohort*

Start age (years)	OPT costs (£)	OPT QALYs	CRT-P costs (£)	CRT-P QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
30	23,967	7.29	46,602	9.10	22,634	1.81	12,506
40	23,318	7.11	45,139	8.81	21,821	1.70	12,819
50	21,551	6.62	41,622	8.11	20,071	1.49	13,469
60	17,019	5.35	33,954	6.54	16,936	1.19	14,257
70	11,735	3.81	25,475	4.76	13,740	0.95	14,453
80	8,420	2.82	19,807	3.55	11,387	0.73	15,639
90	6,635	2.28	16,531	2.83	9,896	0.54	18,206
Mixed	**11,073**	**3.60**	**24,208**	**4.47**	**13,134**	**0.88**	**15,008**

TABLE 89 *Undiscounted base case cost-effectiveness results per person for CRT-D compared with OPT (lifetime time horizon), by age and mixed age cohort*

Start age (years)	OPT costs (£)	OPT QALYs	CRT-D costs (£)	CRT-D QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
30	23,967	7.29	62,655	9.95	38,688	2.66	14,537
40	23,318	7.11	60,856	9.61	37,538	2.50	15,038
50	21,551	6.62	56,606	8.79	35,054	2.17	16,175
60	17,019	5.35	47,777	7.07	30,758	1.72	17,904
70	11,735	3.81	38,132	5.19	26,397	1.38	19,118
80	8,420	2.82	31,471	3.87	23,051	1.05	21,994
90	6,635	2.28	27,611	3.05	20,975	0.77	27,228
Mixed	**11,073**	**3.60**	**36,570**	**4.87**	**25,497**	**1.26**	**20,167**

TABLE 90 *Undiscounted base case cost-effectiveness results per person for CRT-D compared with CRT-P (lifetime time horizon), by age and mixed age cohort*

Start age (years)	CRT-P costs (£)	CRT-P QALYs	CRT-D costs (£)	CRT-D QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
30	46,602	9.10	62,655	9.95	16,053	0.85	18,852
40	45,139	8.81	60,856	9.61	15,717	0.79	19,795
50	41,622	8.11	56,606	8.79	14,984	0.68	22,133
60	33,954	6.54	47,777	7.07	13,822	0.53	26,076
70	25,475	4.76	38,132	5.19	12,656	0.43	29,434
80	19,807	3.55	31,471	3.87	11,664	0.32	36,458
90	16,531	2.83	27,611	3.05	11,080	0.23	48,849
Mixed	**24,208**	**4.47**	**36,570**	**4.87**	**12,362**	**0.39**	**31,769**

Compliance of the joint industry submission (CARE-HF-based analysis)[a] with NICE methodological guidance

Aspect of method	NICE methodological requirement	Compliance of submission?
Defining the decision problem	Estimating the clinical effectiveness and cost-effectiveness should begin with a clear statement of the decision problem, in terms of: • technologies being compared • the relevant patient group(s) This statement should be consistent with the Institute's scope for the appraisal	No clear statement, but implicitly the same technologies and patient group as the CARE-HF trial
Perspective	For outcomes, "include all direct health effects whether for patients or, where relevant, other individuals (principally carers)" For costs, an NHS and Personal Social Services (PSS) perspective should be adopted	Yes – NHS perspective (i.e. health gains to individual patients, and NHS costs)
Type of economic evaluation	Cost-effectiveness analysis = the appropriate form of evaluation Health effects should be expressed in QALYs	Yes – incremental cost per QALY estimated
Time horizon	Horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies compared	Probably insufficient – the time horizon is not explicitly justified, and given that over half (53%) of OPT patients and almost two-thirds (65%) of CRT patients are still alive at 5 years, this suggests that a longer time horizon for the base case analysis is needed (particularly because the cost of pulse-generator replacements would probably accrue at and beyond the 5-year time point)
Synthesis of evidence on outcomes	The analysis of clinical effectiveness should consider the: • range of typical patients • normal clinical circumstances • clinically relevant outcomes • comparison with relevant comparators The analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty, and data from all relevant studies. Any systematic review of outcomes should therefore: • describe the process of identifying relevant studies • describe study selection and data extraction methods • describe any critical appraisal tools used	The economic evaluation only made use of clinical effectiveness evidence from one RCT (the CARE-HF trial), despite the availability of a published meta-analysis of CRT effectiveness which included the two most recent and large trials (Freemantle *et al*., 2006,[66] 8 trials, pooled data from $n = 3380$ patients) They justify the reliance of their analyses on the CARE-HF and COMPANION trials on the basis of stated methodological weaknesses of the early CRT trials (p. 11) The range of typical patients and clinical circumstances in these trials (e.g. age and sex, NYHA class mix, diagnostic test inclusion criteria) seem comparable to those who would be considered for CRT in the NHS setting in England and Wales

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
	• identify probable treatment effect modifiers Meta-analysis (statistically pooled estimates of outcomes) is appropriate where there are sufficient relevant and valid data that use measures of outcome that are comparable	They extract the following study outcomes from the CARE-HF study for use in the economic analysis: age and sex, initial NYHA class, QoL score, drugs, probabilities of changing NYHA class, mortality and hospitalisation rates The submission summarises the statistically significant findings of the three existing published meta-analyses
Valuing health effects	Health effects should be valued as QALYs: as quantified using "a standardised and validated (non-disease-specific) instrument" for measuring health-related QoL In turn, "the value of changes in patients' health-related QoL (i.e. utilities) should be based on public preferences elicited using a choice-based method" Evidence should be presented with any data taken from the literature identified systematically	Yes – health effects in the decision model were valued as QALYs Utility values were apparently attached to each of the NYHA classes (I, II, III, and IV). The utility values themselves were derived from the CARE-HF trial MLWHF scores using a regression equation that related them to CARE-HF EQ-5D scores (p. 31 and Leyva *et al.*'s unpublished paper; and using the UK 'tariff' of social preference weights) However, there is no table or other statement of the exact utility values attached to each NYHA class
Evidence on costs	Costs should relate to resources that are under the control of the NHS and PSS, and where differential effects on costs between the technologies being compared are possible These resources should be valued using the prices relevant to the NHS and PSS (where the actual price paid differs from the public list price, the public list price should be used; sensitivity analysis should assess the implications of variations from this price) The Institute should be made aware of any situations where taking a broader perspective – that is, documenting differential impact on non-NHS or non-PSS costs – is justified	Yes – direct medical costs from an NHS perspective. Resource use data for the decision model was obtained from either the CARE-HF trial (time to next hospitalisation) or the Good Hope Hospital, Birmingham (length of stay for implantation, device revision rate, re-implantation rate, unsuccessful implant probability) NHS Reference Cost unit costs were used for: all-cause hospitalisation and device revision [although the exact source of the hospitalisation costs, £198 and £181, are not clear – i.e. which HRG(s)]. Cost of implantation used was the local Good Hope Hospital cost (£8106 including follow-up costs for 12 months) Cost of "re-implantation" considerably higher than cost of "revision", but a full definition of what these two classes of complication include is not specified (e.g. lead displacements, lead infections?) Drug costs were from the World Standard Drug Database (rather than the BNF) Table 2 presented unit costs and sources
Discounting	For the reference case, an annual discount rate of 3.5% should be used for both costs and effects When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0% and 6%	Yes – both costs and QALYs at 3.5% per year Sensitivity analysis varied the discount rate, but since the relevant diagram was not provided we do not know how significant its impact was on the cost–utility estimate. The undiscounted results, however, are presented (in Leyva *et al.*, Table 4)

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Modelling methods	The models should "follow accepted guidelines", including full documentation and justification of structural assumptions and data inputs Also, PSA should be conducted on models to reflect the combined implications of uncertainty in parameters	A discrete event simulation (DES) model, using a hypothetical cohort of 1000 people of mixed age, gender, and initial NYHA class. The DES was conducted in ARENA® software The structure of the model is unclear (Figure 1 of Leyva *et al*. was not supplied), but the main events simulated appear to be changes in NYHA status, CRT revision or re-implantation, all-cause hospitalisation and death No PSA was conducted
Presentation: data values used and their sources	All data used to estimate clinical and cost-effectiveness should be presented in tabular form and include details of data sources For continuous variables, mean values should be presented and used For all variables, measures of precision should be detailed For PSA, the distributions used to characterise the uncertainty in input parameters should be defined and justified	No tabular presentation of all input data Mean values and sources of most input parameters are presented, but not with any measures of precision Validity of some unit costs data difficult to judge (e.g. hospitalisations, and nature of treatment for CRT "Revisions")
Presentation: expected cost-effectiveness results	The expected value of each component of cost and expected total costs should be presented Expected QALYs for each option compared in the analysis should be presented ICERs should be calculated and presented as appropriate (i.e. using standard decision rules)	Adequate tabular presentation of base case results (QALYs, costs and incremental cost per QALY; both discounted and undiscounted)
Presentation: parameter uncertainty in the CEA	PSA should be carried out Confidence ellipses and scatter plots on the cost-effectiveness plane and CEACs are the most appropriate ways of presenting this decision uncertainty	No PSA is presented
Presentation: other forms of uncertainty	E.g. uncertainty about: the choice of studies included in any meta-analysis; the structural assumptions in the model Each alternative analysis should present separate probabilistic results	A one-way sensitivity analysis is presented, but only in terms of the impact on total and incremental cost. No sensitivity analysis in relation to either QALYs or incremental cost per QALY (Figure 4 was missing)
Presentation: analyses of patient subgroups	Where appropriate[b], there should be separate estimates of clinical effectiveness and cost-effectiveness for each relevant[b] patient subgroup E.g. A 'per-protocol' (trial) subgroup analysis may be valid in addition to the ITT analysis of clinical effectiveness	The only analysis of patient subgroups was the one-way sensitivity analysis, and the impact on incremental costs of: NYHA class mix (either all NYHA III or all NYHA IV), age, sex

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Reflecting equity considerations in CEA	In the reference case, an additional QALY should receive the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs weighted equally regardless of the characteristics of the individuals simulated

[a] The document against which compliance with NICE methodological guidance was judged is the 61-page Combined Industry Submission to NICE dated 18 May 2006, and in particular Section 4.3.1 (pp. 31–32) on cost-effectiveness. Where necessary this was supported by reference to the separately submitted, more detailed paper of the same analysis by Leyva and colleagues (NB: the figures and tables for this paper were missing).
[b] Where capacity to benefit from treatment and/or costs is likely to differ (based on clear clinical justification, or biological plausibility).

Compliance of joint industry submission for CRT-P and CRT-D (5-year UK and COMPANION-based analysis)[a] with NICE methodological guidance

Aspect of method	NICE methodological requirement	Compliance of submission?
Defining the decision problem	Estimating the clinical and cost-effectiveness should begin with a clear statement of the decision problem, in terms of: • technologies being compared • the relevant patient group(s) This statement should be consistent with the Institute's scope for the appraisal	Yes – the stated goals of the submitted model-based economic analysis were: 1. to estimate the cost-effectiveness of CRT-P and CRT-D vs OPT in HF patients eligible for CRT 2. to estimate the NHS budget impact of CRT adoption scenarios The patient group is implicitly the same as those entered in the COMPANION trial, which is broadly consistent with those in the NICE scope for the appraisal. The US analysis was adapted by applying UK costs for hospitalisations and therapy delivery
Perspective	For outcomes, "include all direct health effects whether for patients or, where relevant, other individuals (principally carers)" For costs, an NHS and PSS perspective should be adopted	Yes – direct health effects on patients, including QoL Yes – direct medical treatment costs to the NHS
Type of economic evaluation	Cost-effectiveness analysis = the appropriate form of evaluation Health effects should be expressed in QALYs	Yes – model-based CEA, producing estimates of incremental cost per QALY

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Time horizon	Horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies compared	Base case analysis was 5 years (i.e. shorter than the typical period for device revision/battery replacement), even though model followed patients for 7 years They partly justify the 5-year time horizon by stating that many of these patients are over 65 years old (rather than on the proportion alive at 5 years)
Synthesis of evidence on outcomes	The analysis of clinical effectiveness should consider the: • range of typical patients • normal clinical circumstances • clinically relevant outcomes • comparison with relevant comparators The analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty, and data from all relevant studies. Any systematic review of outcomes should therefore: • describe the process of identifying relevant studies • describe study selection and data extraction methods • describe any critical appraisal tools used • identify probable treatment effect modifiers Meta-analysis (statistically pooled estimates of outcomes) is appropriate where there are sufficient relevant and valid data that use measures of outcome that are comparable	Simulated patients were equivalent to those in the COMPANION trial, which is the only published trial including a comparison between OPT and CRT-D The clinically relevant outcomes included in the decision model were survival and QoL (utility). They did not report any other clinical event or state-occupancy rates (e.g. number of hospitalisations) There was no systematic review or meta-analysis of outcomes that fed into the decision model. Survival estimates were taken from the COMPANION trial (Feldman *et al.*, 2005[109])
Valuing health effects	Health effects should be valued as QALYs: as quantified using "a standardised and validated (non-disease-specific) instrument" for measuring health-related QoL In turn, "the value of changes in patients' health-related QoL (i.e. utilities) should be based on public preferences elicited using a choice-based method" Evidence should be presented with any data taken from the literature identified systematically	Health effects were valued as QALYs The utility value attached to survival time in each comparator arm in the model was derived from MLHFQ scores from the COMPANION trial (at baseline, 3 and 6 months) and converted to utilities using an algorithm developed by Havranek *et al.*, 1999:[115] $\text{Utility} = 0.02\text{MLHFQ} - 0.000109(\text{MLHFQ})^2$ The Havranek algorithm was based on a sample of 50 HF patients who completed a number of QoL instruments and a time trade-off utility elicitation exercise. The strength of relationship, however, was very weak ($r^2 = 0.1$)

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Evidence on costs	Costs should relate to resources that are under the control of the NHS and PSS, and where differential effects on costs between the technologies being compared are possible These resources should be valued using the prices relevant to the NHS and PSS (where the actual price paid differs from the public list price, the public list price should be used; sensitivity analysis should assess the implications of variations from this price) The Institute should be made aware of any situations where taking a broader perspective – that is, documenting differential impact on non-NHS or non-PSS costs – is justified	The UK costs applied were a mixture of NHS NSRC costs (with US hospital DRGs mapped to NHS HRGs) and device and initial implantation costs from the unpublished paper by Leyva *et al*.
Discounting	For the reference case, an annual discount rate of 3.5% should be used for both costs and effects When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0% and 6%	Yes – both costs and effects
Modelling methods	The models should "follow accepted guidelines", including full documentation and justification of structural assumptions and data inputs Also, PSA should be conducted on models to reflect the combined implications of uncertainty in parameters	Apparently (model not analysed). Process of fitting of exponential survival curves was not fully described. Also, the lack of pathways in the model to reflect separately the incidence of major device-related complications reduces the flexibility of the model to explore the impact of these complication rates A full PSA was conducted
Presentation: data values used and their sources	All data used to estimate clinical effectiveness and cost-effectiveness should be presented in tabular form and include details of data sources For continuous variables, mean values should be presented and used For all variables, measures of precision should be detailed For PSA, the distributions used to characterise the uncertainty in input parameters should be defined and justified	Apart from implantation costs, very few other data inputs were described in this summary report
Presentation: expected cost-effectiveness results	The expected value of each component of cost and expected total costs should be presented Expected QALYs for each option compared in the analysis should be presented ICERs should be calculated and presented as appropriate (i.e. using standard decision rules)	In the short summary report, very little detail is provided on components of total cost and expected QALYs with each comparator

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Presentation: parameter uncertainty in the CEA	PSA should be carried out Confidence ellipses and scatter plots on the cost-effectiveness plane and CEACs are the most appropriate ways of presenting this decision uncertainty	Both the methods and the results of the PSA were fully reported One-way sensitivity analysis was selective (i.e. not all model parameters) but mostly appropriate. The inclusion of only 10% of CRT patients needing battery replacement seems optimistic, particularly with longer time horizons. However, other uncertain assumptions have been made such that they would increase the ICER for CRT
Presentation: other forms of uncertainty	E.g. uncertainty about: the choice of studies included in any meta-analysis; the structural assumptions in the model Each alternative analysis should present separate probabilistic results	Relevant discussion of key issues (e.g. transferability of effectiveness and resource use data from the US to UK healthcare setting) No additional PSA for non-base-case scenarios was presented
Presentation: analyses of patient subgroups	Where appropriate[b], there should be separate estimates of clinical effectiveness and cost-effectiveness for each relevant[b] patient subgroup E.g. A 'per-protocol' (trial) subgroup analysis may be valid in addition to the ITT analysis of clinical effectiveness	No subgroup analyses presented However, their justification for **not** directly comparing the cost-effectiveness of CRT-P and CRT-D is based on the view that clinicians would judge different subgroups of patients to be eligible for each
Reflecting equity considerations in CEA	In the reference case, an additional QALY should receive the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs weighted equally regardless of the characteristics of the individuals simulated

[a] The document against which compliance with NICE methodological guidance was judged is the 61-page Combined Industry Submission to NICE dated 18 May 2006, and in particular Section 4.4.2 (pp. 33–35) on cost-effectiveness. Where necessary this was supported by reference to the separately submitted more detailed report of the same analysis by United Biosource Corporation for Guidant (authors: R Brown and others, dated 16 May 2006).

[b] Where capacity to benefit from treatment and/or costs is likely to differ (based on clear clinical justification, or biological plausibility).

Compliance of industry submission from Guidant[a] for CRT-P and CRT-D (5-year UK-based analysis) with NICE methodological guidance

Aspect of method	NICE methodological requirement	Compliance of submission?
Defining the decision problem	Estimating the clinical and cost-effectiveness should begin with a clear statement of the decision problem, in terms of: • technologies being compared • the relevant patient group(s) This statement should be consistent with the Institute's scope for the appraisal	Yes – the stated goals of the submitted economic analysis were: 1. to estimate the cost-effectiveness of CRT-P and CRT-D vs OPT in HF patients eligible for CRT 2. to estimate the NHS budget impact of CRT adoption scenarios The patient group is implicitly the same as those entered in the CAMPANION trial, which is broadly consistent with those in the NICE scope for the appraisal. The US analysis was adapted by simply applying UK costs for hospitalisations and therapy delivery
Perspective	For outcomes, "include all direct health effects whether for patients or, where relevant, other individuals (principally carers)" For costs, an NHS and PSS perspective should be adopted	Yes – direct health effects on patients, including QoL Yes – direct medical treatment costs to the NHS
Type of economic evaluation	Cost-effectiveness analysis = the appropriate form of evaluation Health effects should be expressed in QALYs	Yes – CEA, producing estimates of incremental cost per QALY
Time horizon	Horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies compared	Only 5 years (i.e. shorter than the typical period for device revision/battery replacement)
Synthesis of evidence on outcomes	The analysis of clinical effectiveness should consider the: • range of typical patients • normal clinical circumstances • clinically relevant outcomes • comparison with relevant comparators The analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty, and data from all relevant studies. Any systematic review of outcomes should therefore: • describe the process of identifying relevant studies • describe study selection and data extraction methods • describe any critical appraisal tools used • identify probable treatment effect modifiers Meta-analysis (statistically pooled estimates of outcomes) is appropriate where there are sufficient relevant and valid data that use measures of outcome that are comparable	Simulated patients were equivalent to those in the COMPANION trial, which is the only published trial including a comparison between OPT and CRT-D The clinically relevant outcomes included in the decision model were survival and QoL (utility) There was no systematic review or meta-analysis of outcomes that fed into the decision model

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Valuing health effects	Health effects should be valued as QALYs: as quantified using "a standardised and validated (non-disease-specific) instrument" for measuring health-related QoL In turn, "the value of changes in patients' health-related QoL (i.e. utilities) should be based on public preferences elicited using a choice-based method" Evidence should be presented with any data taken from the literature identified systematically	Health effects were valued as QALYs The utility value attached to survival time in each comparator arm in the model was derived from MLHFQ scores from the COMPANION trial (at baseline, 3 and 6 months) and converted to utilities using an algorithm developed by Havranek *et al*., 1999:[115] Utility = 0.02MLHFQ – 0.000109(MLHFQ)^2 The Havranek algorithm was based on a sample of 50 HF patients who completed a number of QoL instruments and a time trade-off utility elicitation exercise. The strength of relationship, however, was very weak (r^2 = 0.1)
Evidence on costs	Costs should relate to resources that are under the control of the NHS and PSS, and where differential effects on costs between the technologies being compared are possible These resources should be valued using the prices relevant to the NHS and PSS. (Where the actual price paid differs from the public list price, the public list price should be used; sensitivity analysis should assess the implications of variations from this price) The Institute should be made aware of any situations where taking a broader perspective – that is documenting differential impact on non-NHS or non-PSS costs – is justified	The UK costs applied were a mixture of NHS NSRC costs (with US hospital DRGs mapped to NHS HRGs) and other costs from the unpublished paper by Leyva *et al*.
Discounting	For the reference case, an annual discount rate of 3.5% should be used for both costs and effects When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0% and 6%	Yes – both costs and effects
Modelling methods	The models should "follow accepted guidelines", including full documentation and justification of structural assumptions and data inputs Also, probabilistic sensitivity analysis should be conducted on models to reflect the combined implications of uncertainty in parameters	Apparently (model not analysed). Process of fitting of exponential survival curves was not fully described A PSA was mentioned but not fully reported in this short report
Presentation: data values used and their sources	All data used to estimate clinical effectiveness and cost-effectiveness should be presented in tabular form and include details of data sources For continuous variables, mean values should be presented and used For all variables, measures of precision should be detailed For PSA, the distributions used to characterise the uncertainty in input parameters should be defined and justified	Apart from implantation costs, very few other data inputs were described in this summary report

continued

Aspect of method	NICE methodological requirement	Compliance of submission?
Presentation: expected cost-effectiveness results	The expected value of each component of cost and expected total costs should be presented Expected QALYs for each option compared in the analysis should be presented ICERs should be calculated and presented as appropriate (i.e. using standard decision rules)	In this short summary report, very little detail is provided on components of total cost and expected QALYs with each comparator
Presentation: parameter uncertainty in the CEA	PSA should be carried out Confidence ellipses and scatter plots on the cost-effectiveness plane and CEACs are the most appropriate ways of presenting this decision uncertainty	Although the percentage likelihood of the ICER being less than £20,000 per QALY was reported for both CRT-P and CRT-D, the PSA was not fully reported (neither input parameter values and distributions, nor cost-effectiveness plane scatter plot or CEAC) One-way exploration of parameter uncertainty seemed adequate (but again not fully reported in this report)
Presentation: other forms of uncertainty	E.g. uncertainty about: the choice of studies included in any meta-analysis; the structural assumptions in the model Each alternative analysis should present separate probabilistic results	Some discussion (e.g. transferability of effectiveness and resource use data from the US to UK healthcare setting) No additional PSA for non-base case scenarios
Presentation: analyses of patient subgroups	Where appropriate[b], there should be separate estimates of clinical and cost-effectiveness for each relevant[b] patient subgroup E.g. A 'per-protocol' (trial) subgroup analysis may be valid in addition to the ITT analysis of clinical effectiveness	No subgroup analyses presented However, their justification for **not** directly comparing the cost-effectiveness of CRT-P and CRT-D is based on the view that clinicians would judge different subgroups of patients to be eligible for each
Reflecting equity considerations in CEA	In the reference case, an additional QALY should receive the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs weighted equally regardless of the characteristics of the individuals simulated

[a] The document against which compliance with NICE methodological guidance was judged is the 31-page report from Guidant dated 18 May 2006, and in particular Section 6 (pp. 28–31) on cost-effectiveness.
[b] Where capacity to benefit from treatment and/or costs is likely to differ (based on clear clinical justification, or biological plausibility).

Appendix 8

Ongoing trials

Details of ongoing RCTs of CRT are summarised in *Table 91*.

TABLE 91 *Registered ongoing RCTs of CRT*

	Trial name and registration No.		
	Trip HF NCT00187265	**DECREASE-HF NCT00158951**	**PACMAN NCT00180596**
Aim	To evaluate the feasibility of permanent biventricular pacing using three ventricular leads, and its efficacy in terms of inter and intraventricular resynchronisation, in patients with congestive heart failure and a non-functional atrium (chronic AF)	To demonstrate the safety and effectiveness of the CONTAK® RENEWAL™ 2/4/4HE CRT-D family and EASYTRAK® 2 lead in delivering LV-CRT or BiV-CRT with an LV	To evaluate the benefit of biventricular pacing in patients with HF who were receiving optimal pharmacological therapy, and who were either with or without an ICD indication
Intervention	CRT	CRT-D	CRT
Comparator	Not known	Left ventricular pacing, simultaneous BiV pacing, or sequential BiV pacing	OPT
Inclusion criteria	NYHA class III–IV in spite of optimal medical treatment for their congestive heart failure for 1 month; permanent AF; LVEF 35%; indication for a pacemaker implantation for a permanent and symptomatic bradycardia, or already implanted pacemaker under the condition that leads positioning corresponds to the criteria described in the protocol; aortic pre-ejection delay ⩽140 ms	Met for a CRT-D device, NYHA class III–IV despite optimal pharmacological HF therapy, 12-lead ECG obtained no more than 90 days prior to enrolment documenting a sinus rate >50 bpm, QRS >150 ms and PR interval >320 ms measured from any two leads, and a P-wave duration <150 ms measured from lead V1, creatinine <2.5 mg/dl obtained no more than 14 days prior to enrolment, LVEF <35%	NYHA class III and IV with EF <35%; optimal individual drug therapy in 2 weeks prior to enrolment including ACE inhibitors; β-blockers and diuretics unless not tolerated
Primary outcome(s)	Z-ratio	Combined outcome – peak oxygen consumption and left ventricular end systolic dimension	6-minute walk test at 6 months
Secondary outcomes	Not known	Reduced HF symptoms; stable chronic LV thresholds, R-wave amplitudes and impedances from those not selected in final programming at 6 months	QoL; NYHA classification; incidence of adverse events
Sample size[a]	Not known	360	262
Follow-up	Not known	Up to 1 year	Up to 6 months
Setting	Not known	USA, multicentre	Europe, multicentre

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	Trial name and registration No.		
	Trip HF NCT00187265	**DECREASE-HF NCT00158951**	**PACMAN NCT00180596**
Recruitment:			
Start date	April 2003	May 2003	January 2000
Expected end date	November 2005	October 2004	September 2006
Principal investigator	Prof. J-C Daubert, CHU Pontchaillou, 35011 Rennes, France	Dr DB De Lurgio, Carlyle Fraser Heart Center, Division of Cardiology, Emory University School of Medicine, Atlanta, GA 30365, USA	Dr P Hanrath, Medizinische Klinik I, University RWTH Aachen, Pauwelsstr. 30, 52057 Aachen, Germany
Funder	St Jude Medical	Guidant Corporation	Guidant Corporation
Status	"No longer recruiting"	"No longer recruiting" Protocol published (*J Card Fail* 2005;**11**:233–9)	"No longer recruiting"
	APAF (Assessment of Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation) NCT00111527	**MADIT-CRT NCT00180271**	**B-LEFT HF NCT00187213**
Aim	Hypothesised that a suboptimal level of resynchronisation is achieved in many patients with actual standards and that some techniques based on tissue-Doppler ECHO could be more effective to obtain better (hopefully optimal) CRT results	To determine if CRT-D will reduce the risk of mortality and HF events by ~25%, in subjects who are in NYHA functional class II with non-ischaemic or ischaemic cardiomyopathy and subjects who are in NYHA functional class I with ischaemic cardiomyopathy, left ventricular dysfunction (EF $\leq$0.30) and prolonged intraventricular conduction (QRS duration $\geq$130 ms)	Hypothesised that patients indicated for an ICD with cardiac resynchronisation therapy respond as well to LV only pacing as to BiV pacing
Intervention	RV apical pacing with delayed CRT	CRT-D	CRT-D BiV pacing
Comparator	Early optimal CRT based on an ECHO stratification	ICD only	CRT-D LV pacing

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	Trial name and registration No.		
	APAF (Assessment of Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation) NCT00111527	**MADIT-CRT NCT00180271**	**B-LEFT HF NCT00187213**
Inclusion criteria	Permanent AF in whom a clinical decision had been made to undertake complete AV junction ablation and ventricular pacing because of drug-refractory, severely symptomatic, uncontrolled high ventricular rate Patients with permanent AF, drug-refractory HF, depressed LV function in whom a clinical decision had been made to undertake left ventricular synchronisation pacing	NYHA class I or II for the past 3 calendar months prior to and at the time of enrolment; one or more clinically documented (Q wave or enzyme positive) prior MIs, but not within 3 calendar months of enrolment and/or one or more prior coronary artery bypass graft surgeries or percutaneous coronary interventions (balloon and/or stent angioplasty) but not within 3 calendar months of enrolment Or Non-ischaemic heart disease including dilated cardiomyopathy characterised by a low EF and increased ventricular volume, with ventricular compliance that is normal or increased, NYHA class II for the past 3 calendar months prior to and at the time of enrolment; **and** all of the following: stable optimal pharmacological therapy, EF $\leqslant$0.30 by angiographic, radionuclide, or ECHO methods within 1 year prior to enrolment and measured during the enrolment ECHO obtained within 14 days prior to randomisation to confirm eligibility (recommended); resting QRS duration $\geqslant$130 ms on printout of a current ECG obtained within 14 days prior to randomisation; sinus rhythm by ECG (including RBBB and first-degree heart block with PR <250 ms)	Approved indication for implantation of ICD, NYHA classification of III or IV despite receiving a minimum of 30 days of stable optimal pharmacological therapy; ventricular conduction delay >130 ms; ventricular end diastolic manifested as a QRS >55 mm; LVEF $\leqslant$35%
Primary outcome(s)	Short term (6 months): QoL (MLWHF), NYHA classification and exercise capacity; long-term (24 months): composite end-point of: death due to cardiovascular cause, hospitalisation for worsening HF, worsening HF or failure to achieve a persistent subjective symptom improvement (clinical failure)	Combined endpoint of all-cause mortality or HF events	Functional capacity and reverse remodelling

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	Trial name and registration No.		
	APAF (Assessment of Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation) NCT00111527	**MADIT-CRT NCT00180271**	**B-LEFT HF NCT00187213**
Secondary outcomes	Evaluation of the predictive value of ECHO desynchronisation indexes (inter- and intra-LV delays) for identification of clinical failure (see above); Cost–benefit comparison of the 2 pacing strategies	1. Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to 1 year in ECHO-determined left ventricular internal volume at end systole with CRT therapy turned off during the 1-year echocardiogram 2. Evaluate the effects of CRT-D, relative to ICD-only, on the changes from baseline to 1 year in ECHO-determined left ventricular internal volume at end diastole with CRT therapy turned off during the 1-year echocardiogram 3. Evaluate the effects of CRT-D, relative to ICD-only, on the subject-specific rates of multiple HF events over the full study period	Proportion of improved patients (heart failure clinical composite response)
Sample size[a]	458	1820	172
Follow-up	Up to 24 months	Not known	6 months
Setting	Not known	USA and international, multicentre	International, multicentre
Recruitment: Start date Expected end date	 May 2005 May 2008	 December 2004 Not known	 December 2004 March 2007
Principal investigator	Dr M Brignole, Lavagna, Genova, Italy	Dr AJ Moss, University of Rochester, Rochester NY, USA	Dr C. Leclercq, Department of Cardiology, CHU Pontchaillou, 35011 Rennes, France
Funder	Arcispedale Santa Maria Nuova Medtronic	Guidant Corporation	St Jude Medical
Status	"Currently recruiting"	"Currently recruiting" Protocol published [*Ann Noninvasive Electrocardiol* 2005;**10**(4 Suppl):34–43]	"Currently recruiting" Protocol published (*Europace* 2006;**8**:76–80)

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	Trial name and registration No.		
	An-Art Study AV-Node Ablation in Cardiac Resynchronisation Therapy NCT00260546	**PEGASUS CRT NCT00146848**	**RAFT (Resynchronization/Defibrillation for Advanced Heart Failure Trial) NCT00251251**
Aim	To investigate whether patients with a CRT-P or CRT-D will benefit from an AV node ablation compared to a CRT alone	To assess the effect of a CRT-D device programmed to DDD-70 or DDDR-40 compared to a CRT device programmed to DDD-40 in heart failure patients	To compare if CRT-P and CRT-D devices will reduce total mortality and hospitalisation for CHF
Intervention	CRT-P or CRT-D	CRT-D in 3 pacing modes	CRT-P or CRT-D
Comparator	CRT-P or CRT-D, followed by AV node ablation	As above	OPT
Inclusion criteria	All patients who had a CRT-P or CRT-D and who are under optimal medical therapy	Meet current indications for CRT-D device, are in sinus rhythm at the time of implant, on optimal pharmacologic therapy or have developed a recent ICD indication that necessitates ICD therapy concurrent with the optimisation of pharmacologic therapy	NYHA class II or class III LVEF ⩽30% or LVEF ⩽30% and LV end diastolic dimension ⩾60 mm within 6 months prior QRS complex width ⩾120 ms or paced QRS measurement ⩾200 ms ICD indication for primary or secondary prevention Optimal heart failure pharmacological therapy Normal sinus rhythm or chronic persistent atrial tachyarrhythmia with resting ventricular heart rate ⩽60 bpm and 6-minute hall walk ventricular heart rate of ⩽90 bpm or chronic persistent atrial tachyarrhythmia with resting ventricular heart rate >60 bpm and 6-minute hall walk ventricular heart rate of >90 bpm and booked for atrio-ventricular junction ablation
Primary outcome(s)	Percentage of biventricular stimulated heart cycles	Clinical composite score (death, heart failure hospitalisation, NYHA class, Global Assessment rating)	Composite of all-cause total mortality and hospitalisation for CHF
Secondary outcomes	Combined end-point of worsening of HF, NYHA class, 6-minute walking distance and hospitalisation for HF, death or heart transplantation	Quality of life, physical activity, atrial arrhythmias, ventricular arrhythmic events, medications, and programming changes	Total mortality; cardiovascular mortality; sudden arrhythmic death; progressive HF death; all-cause hospitalisation rate; CHF hospitalisation rate; health-related QoL; cost-effectiveness

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	Trial name and registration No.		
	An-Art Study AV-Node Ablation in Cardiac Resynchronisation Therapy NCT00260546	**PEGASUS CRT NCT00146848**	**RAFT (Resynchronization/Defibrillation for Advanced Heart Failure Trial) NCT00251251**
Sample size[a]	125	1200	1500
Follow-up	Not known	Not known	Not known
Setting	Not known	Not known	Not known
Recruitment: Start date Expected end date	 November 2005 July 2007	 December 2004 Not known	 April 2003 August 2008
Principal investigator	Dr C Sticherling, Cardiology, University Hospital Basel, Switzerland	Dr DO Martin, Cleveland Clinic Hospital, Cleveland, OH 44195, USA	Dr A Tang, University of Ottawa Heart Institute, Ottawa, Ontario K1Y 4 W7, Canada
Funder	University Hospital, Basel, Switzerland	Guidant Corporation	University of Ottawa Heart Institute Canadian Institutes of Health Research (CIHR) Medtronic
Status	"Not yet open for patient recruitment"	"Currently recruiting"	"Currently recruiting"
	Biopace NCT00187278	**Progressive Ventricular Dysfunction Prevention in Pacemaker Patients NCT00170326**	**ADVANCE CRT-D NCT00147290**
Aim	The compare BiVP vs RV pacing	To evaluate the progression of ventricular dysfunction in patients with ventricular dysfunction within the permanent pacing population	To compare the efficacy of RV and BiV antitachycardia pacing (ATP) for the termination of ventricular arrhythmias in patients who are candidates to a CRT and have a class I or IIA indication for ICD implantation
Intervention	CRT-P	BiVP	BiV ATP
Comparator	RV pacing	Conventional pacing	RV pacing

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	Trial name and registration No.		
	Biopace NCT00187278	**Progressive Ventricular Dysfunction Prevention in Pacemaker Patients NCT00170326**	**ADVANCE CRT-D NCT00147290**
Inclusion criteria	Presence of an indication for ventricular pacing according to the actual guidelines for the implantation of cardiac pacemakers and a need for frequent (or even permanent) ventricular pacing	Meet class I and/or class IIa implantation criteria for permanent cardiac pacing according to the guidelines given by the ACC/AHA	All patients with class I and IIa indications for an ICD implantation and CRT
Primary outcome(s)	Not known	Evolution of the EF of the LV and the ventricular volumes	Termination of ventricular tachyarrhythmia
Secondary outcomes	Not known	Combined end-point of cardiac mortality, appearance of and hospitalisation due to cardiovascular problems; morbidity; necessity for or changes in medication due to heart failure: ACE inhibitors, β-blockers and/or diuretics; appearance of or worsening of mitral insufficiency	Not known
Sample size[a]	Not known	100	400
Follow-up	Not known	Not known	12-months
Setting	Not known	Not known	Not known
Recruitment: Start date Expected end date	 Not known Not known	 December 2002 December 2007	 February 2004 2007
Principal investigator	Dr R Funck, Klinikum der Philipps-Universität Marburg, Germany	Dr JO Schwab, Department of Medicine–Cardiology, University of Bonn, Bonn, Germany	Dr A Tang, University of Ottawa Heart Institute, Ottawa, Ontario K1Y 4 W7, Canada
Funder	St Jude Medical	Medtronic	University of Ottawa Heart Institute Canadian Institutes of Health Research (CIHR) Medtronic
Status	"Currently recruiting"	"Currently recruiting"	"Currently recruiting"

continued

TABLE 91 *Registered ongoing RCTs of CRT (cont'd)*

	REVERSE
Aim	To establish whether CRT combined with optimal medical treatment can attenuate HF disease progression compared with optimal medical treatment alone in patients NYHA class I and II
Intervention	CRT On
Comparator	CRT Off
Inclusion criteria	Asymptomatic LV dysfunction ± NYHA class I ACC/AHA stage C or NYHA class II HF, QRS duration ⩾ms, LVEF ⩽0.40 and LVEDV ⩾55 mm
Primary outcome(s)	HF clinical composite response
Secondary outcomes	Ventricular end-systolic volume index
Sample size[a]	500
Follow-up	Up to 5 years
Setting	International, multicentre
Recruitment: Start date Expected end date	 September 2004 2006
Principal investigator	Dr C Linde, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden
Funder	Medtronic
Status	Not known. Protocol published (*Am Heart J* 2006;**151**:288–94)

[a] Total number of intervention and control patients.

Other ongoing CRT trials.

Evaluation of resynchronization therapy for heart failure (EARTH)

ISRCTN	ISRCTN42560370
Title of trial/grant title	Evaluation of resynchronization therapy for heart failure (EARTH)
Acronym	EARTH
Serial number at source	UCT-67914
Study hypothesis	The primary hypothesis of the LESSER-EARTH is that HF patients with an indication for an ICD without a prolonged QRS duration will benefit clinically from resynchronization therapy. The primary hypothesis of the GREATER-EARTH is that HF patients with an indication for an ICD and for CRT will benefit better clinically with LV-based CRT than with BiV-based CRT
Research ethics review	Comité d'Éthique de la Recherche et du Développement des Nouvelles Technologies (11 November 2003) de l'Institut de Cardiologie de Montréal
Study design	RCT
Disease or condition	HF
Participants – inclusion criteria	Diagnosis of asthma verified by primary care MD Asthma managed by primary care MD and receiving asthma drug therapy from primary care MD
Participants – exclusion criteria	1. Indication for permanent pacing or with chronotropic insufficiency defined as follows: severe sinus bradycardia (resting heart rate <50/minute), chronotropic insufficiency, defined as a heart rate during the screening 6-minute walk test that does not increase by more than 10 beats/minute compared with the resting rate, first-degree AV block with a PR interval >250 ms, second- or third-degree AV block, either persistent or intermittent, patients with a pacemaker or an ICD who are paced in either chamber (A or V) more than 5% of time 2. LV dysfunction associated with a reversible cause such as postpartum cardiomyopathy, tachycardia-induced cardiomyopathy, acute myocarditis or acute toxic cardiomyopathy (including acute alcoholic) 3. MI within the past 6 weeks (defined by 2 of the 3 following conditions: prolonged chest pain, ECG changes suggesting of AMI or cardiac enzymes elevation more than twice the local upper limit of normal) 4. Cardiac surgery within the past 6 weeks 5. Coronary angioplasty within the past 6 months 6. Moderate or severe cardiac valve stenosis 7. Inability or a limitation to walk for reasons other than HF symptoms (e.g. angina, intermittent claudication, severe lung condition or arthrosis) 8. Severe coexisting illnesses making survival >6 months unlikely 9. Pregnancy and/or nursing 10. Inability or unwillingness to consent or comply with follow-up requirements 11. Participation in another study
Target number of participants	240

Interventions	1. Insertion of the resynchronization pacing system 2. Control tests to ensure condition is stable and device functioning properly 3a. LESSER-EARTH: patients randomized to resynchronization on versus off. 12-month follow-up 3b. GREATER-EARTH: patients randomized to LV resynchronization versus BiV resynchronization. Crossover 6 months
Primary outcome(s)	Total exercise duration at constant submaximal load (defined as 75% of peak exercise during the baseline metabolic evaluation)
Secondary outcome(s)	Clinical end-points (QoL–NYHA) Electrical end-points (ECG) ECHO end-points (LVEF and volumes) MUGA scan end-points (LVEF and synchrony index) Neuro-hormones (BNP–ANP)
Sources of funding	Canadian Institutes of Health Research (CIHR; http://www.cihr-irsc.gc.ca) Protocol: UCT-67914. St. Jude Medical Canada Inc. (Mississauga, ON, Canada)

Am Heart J 2005;**149**:600–5. Related Articles, Links

Predictors of response to cardiac resynchronization therapy (PROSPECT) – study design

Yu CM, Abraham WT, Bax J, Chung E, Fedewa M, Ghio S, Leclercq C, Leon AR, Merlino J, Nihoyannopoulos P, Notabartolo D, Sun JP, Tavazzi L; PROSPECT Investigators
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BACKGROUND: Cardiac resynchronization therapy (CRT) is currently indicated in patients with moderate to severe heart failure, a wide QRS complex and significant left ventricular dysfunction despite optimal medical therapy. Adoption of these criteria for CRT results in a favorable response in only two thirds of candidates. METHODS: "Predictors of response to cardiac resynchronization therapy (PROSPECT)", a prospective, multicenter, nonrandomized study, aims to identify echocardiographic measures of dysynchrony and evaluate their ability to predict response to CRT. PROSPECT will enroll approximately 300 patients in up to 75 centers in the United States, Asia, and Europe with clinical follow-up for 6 months. We will prospectively and individually test a variety of conventional echocardiographic and tissue Doppler imaging parameters against measures of clinical response. The primary response criteria are improvement in the heart failure Clinical Composite Score and left ventricular reverse remodeling. Enrollment began in March 2004 and is expected to conclude early 2005

Am Heart J 2006;**151**:288–94. Related Articles, Links

Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic left ventricular dysfunction with previous symptoms or mild heart failure – the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study

Linde C, Gold M, Abraham WT, Daubert JC; REVERSE Study Group
Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden. cecilia.linde@medks.ki.se

BACKGROUND: Cardiac resynchronization therapy (CRT) improves symptoms, reduces heart failure (HF)-related hospitalizations, and reverses left ventricular remodeling in some patients with moderate to severe HF and ventricular dysynchrony defined by a prolonged QRS duration. The effects of CRT on HF outcomes in patients with asymptomatic left ventricular dysfunction (ALVD) or mild HF remain to be determined. METHODS: The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study is a prospective, multicenter, randomized, double-blind, parallel, controlled clinical trial designed to establish whether CRT combined with optimal medical treatment can attenuate HF disease progression compared with optimal medical treatment alone in patients with ALVD

± New York Heart Association class I American College of Cardiology/American Heart Association stage C or New York Heart Association class II HF, QRS duration > or =120 milliseconds, left ventricular ejection fraction < or =0.40, and left ventricular end-diastolic diameter > or =55 mm. The primary end point is the HF clinical composite response and left ventricular end-systolic volume index is the first-order secondary end point. Approximately 500 patients from 100 centers in the United States, Canada, and Europe will be randomized to CRT versus no CRT. The follow-up is 5 years in total with the primary and first secondary end points reported at 12 months. Enrollment began in September 2004 and is expected to be completed in 2006. CONCLUSION: REVERSE will assess the safety and efficacy of CRT in patients with ALVD or mild HF and electrocardiographic evidence of ventricular dysynchrony.

Appendix 9

The protocol

Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Protocol
March 2006

1. Project title: Cardiac resynchronisation (biventricular pacing) for the treatment of heart failure

2. TAR team PenTAG

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3. Plain English summary

This project will review the evidence for the use of cardiac resynchronisation therapy, a method for improving the pumping action of the heart in people with heart failure. It will consider the two versions of this therapy: the first uses a special pacemaker to improve the coordination with which the heart beats, the second has an additional function which can reset the rhythm of the heart if there is a dangerous change in rhythm by delivering an electric shock to restore the normal pattern of beating. The assessment report will draw together all relevant evidence on cardiac resynchronisation therapy in a systematic review. It will also assess whether this therapy is likely to be considered good value for money for the NHS.

4. Decision problem

Purpose

To assess the clinical and cost-effectiveness of cardiac resynchronisation therapy (CRT) also known as biventricular pacing (BVP), with and without an implantable cardioverter defibrillator (ICD), for the treatment of heart failure due to left ventricular systolic dysfunction (LVSD).

Cardiac resynchronisation

The term cardiac resynchronisation therapy (CRT) is taken to be synonymous with the term biventricular pacing (BVP).

Cardiac resynchronisation therapy aims to restore synchronous cardiac contraction by delivering electrical impulses to the right atrium and both ventricles. The result is that both ventricles beat in synchrony, thus improving the efficiency of the heart and reducing the symptoms of heart failure.

Cardiac resynchronisation therapy consists of inserting a pulse generator under the skin (usually) in the upper chest from which three leads pass transvenously into the heart. Two leads are secured in the right atrium and the right ventricle, with the third directed to the left ventricle usually via the coronary sinus. This type of device is known as CRT-P. If an automatic implantable cardioverter defibrillator (ICD) is included the device is known as a CRT-D. After the atria contract, both ventricles are paced to contract at the same time, causing the heart to contract in a more efficient manner, resulting in improved cardiac function.

CRT devices are marketed in the EU by a number of medical device companies: Biotronik, ELA Medical, Guidant, Medtronic, Sorin and St Jude Medical.

The risks and complications of CRT are similar to those of conventional pacing implant. Additionally people may incur: coronary sinus dissection/perforation (approximately 1%),[86] lead dislodgement (approximately 5%)[6] and the risks associated with the use of intravenous contrast media. In all, there has been a device failure rate of approximately 8%.[114]

In the UK, about 1200 CRT devices were implanted in 2005. Numbers are growing at about 40% per year (personal communication from manufacturer).

A recent systematic review of trials using CRT has shown that in the selected people with heart failure when compared with optimal medical therapy alone, CRT reduced all-cause mortality and the risk of hospitalisation and improves people's health-related quality of life.[49] More recently, the CARE-HF study, a large RCT of CRT-P, also demonstrated that CRT without ICD produces a substantial absolute risk reduction of death and reduction in hospitalisations for heart failure, and improved quality of life.[71]

The place of cardiac resynchronisation therapy in the management of heart failure

Heart failure is a clinical syndrome caused by a reduction in the heart's ability to pump blood around the body. Heart failure occurs as the result of the loss of normal functioning of the ventricles of the heart. The ventricles should pump at the same time and in synchrony with the heart's upper chambers (atria). If the contractions lack synchrony, either within or between the ventricles, or between the atria and ventricles, the heart becomes less efficient as a pump. The central problem is of delay in activation of the left ventricle, since this reduces the efficiency of an already damaged pump. This may lead to inefficient pumping of blood to the body and a range of symptoms including shortness of breath, swelling in the ankles or legs, weight gain and fatigue ('heart failure'). The diagnosis of heart failure can be confirmed by a number of tests including chest X-ray, electrocardiogram (ECG), echocardiography (ECHO), radionuclide ventriculography, angiography, as well as blood tests such as natriuretic peptides.

Cardiac function is commonly assessed by measurement of the left ventricular ejection fraction (LVEF). This is the amount of blood ejected from the left ventricle during a single beat expressed as a percentage. Other analysis may include the width and shape of the QRS complex of an ECG waveform which gives an indication of the delay in electrical activation of the ventricles. People with a broad QRS complex often have dyssynchronous (inefficient) contraction of the left ventricle (and dyssynchrony between the right and left ventricles). Intraventricular conduction abnormalities are found in about 30% of people with moderate to severe heart failure.[8] This may result in dyssynchronous contraction which is mechanically inefficient, causing an uneven heart workload, altering the blood flow and metabolism. This lack of heart synchrony results in a fall in the LVEF, thereby increasing the severity of heart failure.[148]

Heart failure impacts on almost all aspects of the quality of life, but particularly mobility.[128] People with heart failure are susceptible to sudden death.[10] There is evidence that the wider the QRS complex, the worse is the prognosis.[149]

Symptoms of heart failure can be described using the New York Heart Association (NYHA) classification:

- **Class I:** No limitations. Ordinary physical activity does not cause fatigue, breathlessness or palpitation. (Asymptomatic left ventricular dysfunction is included in this category.)
- **Class II:** Slight limitation of physical activity. Such people are comfortable at rest. Ordinary

physical activity results in fatigue, palpitation, breathlessness or angina pectoris (symptomatically 'mild' heart failure).
- **Class III:** Marked limitation of physical activity. Although people are comfortable at rest, less than ordinary physical activity will lead to symptoms (symptomatically 'moderate' heart failure).

Current management

Heart failure is currently treated with a range of measures including lifestyle changes, e.g. increased exercise, giving up smoking and reducing alcohol intake. Drug therapy is used in the vast majority of cases and may include:

- β-blockers, to reduce excessive sympathetic stimulation
- angiotensin-converting enzymes (ACE) inhibitors, to improve ventricular geometry and function
- diuretics, to combat oedema
- digoxin, to regulate heart beat especially in atrial fibrillation
- spironolactone, if resistant to other drug therapy
- vasodilators such as nitrates or hydralazine which reduce ventricular load.[5]

Response to biventricular pacing

A number of studies have indicated that biventricular pacing improves the clinical and echocardiographic symptoms of people with heart failure.[6,71,76,80,89,150–152] A positive response to CRT could include an increase in LVEF, reverse left ventricular remodelling and improvements to inter and intraventricular dyssynchrony.

Relevant comparators

- optimal medical therapy alone
- or the alternative CRT device, i.e. CRT-P vs CRT-D.

Population and relevant subgroups

The population for this study are those people with heart failure (from any NYHA class) who have cardiac dyssynchrony and LVSD.

About 900,000 people in England and Wales have heart failure, of whom at least half have LVSD.[13] People with LVSD tend to be younger than the general population of people with heart failure.[1] It is difficult to determine the death rate from heart failure, because of the way in which death is reported in the UK: the 4% of deaths recorded in the UK due to heart failure are an underestimate if heart failure is regarded as a cause of death rather than a mode of death.[11] One-year survival in a survey in Hillingdon, London, in 1995 was 62% (comparable to colonic cancer but less favourable than current breast, prostate or bladder cancer survival rates), with a mortality rate after the first year of around 8–10% per year.[12]

Heart failure causes about 5% of hospital admissions[2] and costs an estimated £716 million in the UK each year, of which about 70% is due to hospitalisation. Hospital admissions are projected to rise by 50% in the next 25 years.[5] Of those who survive their first admission, one-third will die in the subsequent year.[31]

It is estimated that 20–30% of people with NYHA class III/IV chronic heart failure have sufficiently low LVEF and prolonged QRS duration to be potential candidates for CRT.[18] This constitutes between 4200 and 8400 people in England and Wales.[18]

Indications for cardiac resynchronisation therapy

The NICE Heart Failure Guideline (2003) recommends that resynchronisation therapy should be considered for people with LVSD (LVEF $\leq$35%), drug refractory symptoms and a QRS duration >120 ms.[5]

Subgroups

Potential subgroups, depending on the quality of data available, will include:

- age
- atrial fibrillation
- NYHA class
- degree of LVSD, i.e. % LVEF
- degree of dyssynchrony, i.e. QRS duration
- ischaemic and non-ischaemic heart failure.

Key factors to be addressed

- clinical effectiveness
- cost-effectiveness
- adverse events
- quality of life.

Clinical outcomes

- progressive heart failure mortality
- non-heart failure mortality
- all-cause mortality
- heart failure hospitalisations
- exercise capacity
- NYHA class before and after treatment
- adverse effects of treatment
- health related quality of life.

Further considerations

- Dependent on data quality and availability, a separate analysis will be carried out for people who are likely to require a CRT-P and those likely to require a CRT-D, in order to inform guidance on which people should be considered for which intervention.
- Epidemiological estimates of numbers of patients in each subgroup and of the number already treated will be required.
- Implications for implantation, i.e. staffing and technical support levels and other facilities in secondary care, may need to be considered.
- The role of echocardiography in assessing LVSD and therefore affecting the cost effectiveness of interventions will be investigated.

Areas outside this assessment

This assessment will not consider a comparison of CRT devices with stand-alone ICD devices. ICD devices have recently been the subject of NICE guidelines.[59]

5. Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of cardiac resynchronisation. The review will be undertaken systematically following the general principles published by the NHS Centre for Reviews and Dissemination.[60] The research protocol will be updated as necessary as the research programme progresses. Any changes to the protocol will be reported to NCCHTA and NICE.

Search strategy

Refer to Appendix 1a for details of the sources to be searched and the draft search strategy for MEDLINE. No language restriction will be applied to the search strategy. (This has not been included in the report version; see Appendix 2 for the full search strategy.)

The search strategy will comprise the following main elements:

- searching of electronic databases
- Internet
- scrutiny of bibliographies of included studies
- contact with device manufacturers through NICE
- contact with experts in the field.

Study selection criteria and procedures

Types of studies to be included

For the reviews of clinical effectiveness, only systematic reviews of RCTs and single RCTs will be included. These criteria may be relaxed for consideration of adverse effects, for which observational studies may be included.

Population

These will be people with a diagnosis of heart failure, showing cardiac dyssynchrony and LVSD.

Intervention

Cardiac resynchronisation therapy consists of inserting a pulse generator implanted under the skin (usually) in the upper chest from which three leads pass transvenously into the heart. Two of the leads are secured in the right atrium and the right ventricle, as in traditional pacemakers, with the third directed to the left ventricle, usually via the coronary sinus. This type of device is known as CRT-P; an automatic implantable cardioverter defibrillator (ICD) can be included in the device when it is know as a CRT-D.

Comparators

- optimal medical therapy alone
- or the alternative CRT device i.e. CRT-P vs CRT-D.

Subgroups to be examined

Potential subgroups, depending on the quality of data available, will include:

- age
- atrial fibrillation
- NYHA class
- LVEF
- QRS duration Y
- ischaemic and non-ischaemic heart disease.

Outcomes to be examined

- progressive heart failure mortality
- non-heart failure mortality
- all-cause mortality
- heart failure hospitalisations
- exercise capacity
- NYHA class before and after treatment
- adverse effects of treatment
- health-related quality of life.

Types of studies to be excluded

- non-randomised studies (except for adverse events)
- animal models
- preclinical and biological studies

- narrative reviews, editorials, opinions
- reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

Inclusion and exclusion criteria

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of third reviewer when necessary.

Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreement will be resolved by consensus and if necessary a third reviewer will be consulted.

The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No. 4.[60]

Data extraction strategy

Data will be extracted from included studies by one reviewer using a standardised data extraction form (see Appendix 2) and checked by another reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

If meta-analysis is conducted, it will be carried out using fixed and random effects models, using STATA software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic and methods such as meta-regression.

6. Methods for synthesis of evidence from published economic evaluations

(a) Systematic review of cost-effectiveness studies

Search strategy

Refer to Appendix 1b for details of the sources to be searched and the draft search strategy for MEDLINE. No language restriction will be applied to the search strategy. (This has not been included in the report version; see Appendix 2 for the full search strategy.)

The range of sources in the search strategy is the same as for clinical effectiveness.

Study selection criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical with those for the systematic review of clinical effectiveness, except:

Non-randomised studies will be included (e.g. decision model-based analyses or analyses of patient-level cost and effectiveness data alongside observational studies).

Full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.) Stand-alone cost analyses based in the UK NHS will also be sought.

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of third reviewer when necessary.

Study quality assessment

The methodological quality of the economic evaluations will be assessed according to the international consensus-developed criteria list of questions developed by Evers *et al.*[106] Any studies based on decision models will also be assessed against the ISPOR guidelines for good practice in decision analytic modelling.[107]

Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results.

In study design table: author and year; model type or trial based; study design (e.g. CEA, CUA or cost-analysis); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.

For modelling-based economic evaluations a supplementary Study Design table will record further descriptions of: model structure (and note its consistency with the study perspective) and knowledge of disease/treatment processes; sources of transition and chance node probabilities; sources of utility values; sources of resource use and unit costs; handling of heterogeneity in populations; evidence of validation (e.g. debugging, calibration against external data, comparison with other models).

In the Results table: for each comparator we are going to show: incremental cost; incremental effectiveness/utility and incremental cost-effectiveness ratio(s). Excluded comparators on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the reviewers' comments on study quality or generalisability (in relation to the TAR scope) of their results will be recorded.

Synthesis of extracted evidence

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base.

(b) Economic modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and PSS using a decision analytic model. The evaluation will be constrained by available evidence. If possible, the incremental cost-effectiveness of CRT will be estimated in terms of cost per QALY gained.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- the process and main stages of disease, and main outcomes (i.e. knowledge of the natural history of the disease)
- the main patient pathways, in the UK NHS context (both with and without the intervention(s) of interest) and
- those disease states or events that are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from relevant research literature, or our own systematic review of clinical effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submission to NICE.

Resource use will be specified and valued from the perspective of the NHS and PSS in 2004. Cost data will be identified from NHS and PSS reference costs or where these are not relevant they will be extracted from published work and sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

To reflect health-related quality of life, utility values will be sought either directly from relevant research literature or indirectly from quality of life studies.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

The time horizon for our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both cost and outcomes (QALYs) will be discounted at 3.5%.[116]

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper produced by InterTASC (January 2005). In addition to systematic reviews and RCTs, other UK studies will be considered if appropriate.

ICERs estimated from consultee models will be compared with the respective ICERs from the Assessment Group's model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 25 May 2006. Data arriving after this date will not be considered.

Economic evaluations included in the company submissions will be assessed against NICE's guidance on the Methods of Technology Appraisal, and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting existing models or developing *de-novo* modelling.

Any 'commercial-in-confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name, e.g. in brackets).

8. Competing interests of authors

Dr John Dean has undertaken consultancy work and paid presentation for Medtronic, Guidant, St Jude and Biotronik. He is a consultant cardiologist at the Royal Devon and Exeter Foundation NHS Trust.

Dr Rod Taylor has undertaken consultancy work and paid presentation for Medtronic Sarl for a therapy not related to CRT. He is Director of this TAR and working part-time for the Peninsula Medical School.

There are no other competing interests.

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