Association of British Healthcare Industries

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)

Main submission document

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Executive summary

This is a unique, joint submission from all five major device manufacturers (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical) to the NICE clinical and economic appraisal of the use of implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT) for the treatment of cardiac arrhythmias and heart failure (HF) (review of TA95 and TA120). **This submission includes a network meta-analysis of individual patient data (IPD) from over 12,000 patients and 13 randomised clinical trials (RCT), representing the first analysis of its kind and magnitude.**

TA95 found ICD therapy to be both clinically effective and to provide good value for money in secondary prevention of sudden cardiac death. Given the lack of new studies published for this indication and the real term price reduction of an ICD device we have not re-considered this indication in the submission. Hence, we have focused solely on the use of ICD in a primary prevention setting in patients with HF. We have also excluded, for reasons of data paucity, primary prevention ICD use in patients with familial cardiac conditions (long QT syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome etc.).

HF encompasses a very heterogeneous patient population, requiring extensive exploration of different subgroups. Although we have endeavored to be concise, the submission is of necessity an extensive document. Additional material is contained in the appendices which are intended to be used in conjunction with the main submission document.

Overall findings suggest benefit for device treated HF patients (and sub-groups) in all-cause mortality, Health Related Quality of Life (Utility), and cost effectiveness as compared to optimal medical treatment.

We believe this analysis reconfirms the clinical and economic value of ICD, CRT-P, CRT-D in NYHA Class I-IV HF patients.

Background

Heart failure is a major cause of mortality and morbidity, and is responsible for approximately 1 million inpatient bed days annually (2% of all NHS inpatient days), and 5% of medical emergency hospital admissions. Heart failure-related death occurs via two principal mechanisms: sudden cardiac death (usually caused by fatal arrhythmia, and most common in NYHA classes I to III) or progressive HF (most common in NYHA class IV).

Prognosis is poor despite optimal medical therapy. Patients suffer increasing breathlessness and fatigue on exercise and eventually at rest, with consequent impairment of functional ability, health related quality of life, and need for hospitalisation. The goals of treatment are to relieve symptoms and signs, prevent hospital admission, and improve survival. Effective therapies also improve functional capacity and quality of life.

Implantable devices have an established role in the treatment of these patients in addition to optimal medical therapy, with a large body of high quality evidence supporting their safety and efficacy.

- Implantable cardioverter defibrillators (ICD) continuously monitor the heart for arrhythmia and maintain normal heart rate using small, painless electrical signals. They deliver high energy shock therapy (defibrillation) in the event of a potentially life-threatening arrhythmia.
- Cardiac resynchronisation therapy (CRT) uses electrical stimulation to resynchronise the contraction of the ventricles, thereby improving pumping efficiency. Devices that deliver CRT alone are known as CRT-P. While they improve HF symptoms, they do not offer direct protection against sudden cardiac death.
- CRT-D devices combine CRT with a defibrillation function, offering protection from sudden cardiac death in addition to the benefits of CRT.

New evidence has become available since current NICE guidance was published in 2006 (ICDs) and 2007 (CRT), and UK clinical practice has evolved. In addition, device costs have fallen in real terms and battery life has increased. It is therefore to be expected that both clinical recommendations and cost-effectiveness calculations will need to be re-examined at this appraisal.

Device implantation rates vary considerably between cardiac networks within England and Wales: the adjusted annual number of new ICD implants per million population varied from 34 to 131, and annual implantation rates per million for new and replacement CRT devices ranged from 68 to 182/million. The Network Device Survey Group has suggested a minimum annual target of 100 new implants/million population for ICD and 130 total (new + replacement)/million for CRT (CRT-P and CRT-D combined). Current overall rates in England are approximately 72/million and 114/million, respectively, suggesting continuing under-provision and poorer quality care for UK patients compared to other European countries.

Systematic review and network-meta-analysis of individual patient data

A comprehensive systematic review of RCT evidence for clinical effectiveness of OPT (optimal pharmacological therapy), ICD, CRT-P and CRT-D was carried out in accordance with NICE guidelines. 46 articles reporting the results of 22 trials met the criteria for inclusion in the qualitative summary. The review confirms that there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF. This is backed up by several previously published meta-analyses. Additional evidence from long-term follow-up of two studies shows a persistent mortality benefit from both ICD and CRT. No new evidence was identified relating to the use of ICD in a secondary prevention setting.

Individual patient data from over 12,000 patients in 13 clinical trials identified from the systematic review were made available by three Medical Device manufacturers to inform construction of an economic model for this appraisal. This unique collaborative effort resulted in a data set that covered 95% of the patients included in studies identified in the systematic review and followed patients for up to 7.5 years. The power of the IPD approach means the results contained in this document are the best and most robust information available on the impact of CRT and ICD in terms of mortality, health related quality of life and hospitalisations. In particular, the use of IPD has allowed unprecedented exploration of device effects in the widely heterogeneous patient subgroups within HF.

Summary of findings on clinical efficacy

i) Mortality

A baseline risk analysis was conducted in order to predict mortality risk over time for patients receiving OPT (3,477 patients, followed up for up to up to 6.1 years). This analysis found NYHA functional class, ischaemia, QRS duration and LVEF all to be highly significant predictors of survival, along with patient age and gender.

The risk equation developed was able to differentiate between the highly heterogeneous prognoses of patients included in the trials. For patients predicted to be in the upper 20% with respect to survival time, four year survival was [redacted]. For patients predicted to be in the lowest 20%, four year survival was [redacted]

Inclusion of age as a time-dependent covariable in the analysis appeared to produce realistic predictions of survival both within the database follow-up period and when extrapolated over patient lifetime.

A network meta-analysis was conducted including data from all studies identified by the systematic review (12,000+ patients followed up for up to 7.5 years). The analysis found CRT-D to have the strongest effect on all-cause mortality, with a hazard ratio of [redacted] for CRT-D vs. OPT. Treatment effects for the other individual devices were [redacted] for CRT-P vs. OPT and [redacted] for ICD vs. OPT (fixed effects analysis of all trials). These results are similar to those published previously, and support the strong effect of all devices on the all-cause mortality end point.

Given the high level of heterogeneity in the patient groups under consideration, a series of analyses were conducted exploring the impact of patient characteristics on the magnitude of benefit associated with the devices. These analyses identified patients' age, gender and QRS morphology (both QRS duration and the presence of left bundle branch block (LBBB)) to be independently predictive of the magnitude of benefit associated with the devices. Younger patients and male patients appear to benefit more from ICD; but less than other groups from CRT. This is likely to be due to the relatively higher rate of sudden cardiac death relative to other causes in younger and male patients. Patients with a QRS duration of ≥120ms to <150ms benefit more from ICD therapy than those with

shorter or longer QRS durations. Both CRT-P and CRT-D have a stronger impact on mortality in patients with QRS≥150ms and/or LBBB.

ii) Health Related Quality of Life

NYHA class, age, ischemic etiology status, gender and age were all significant (P<0.05) predictors of baseline utility. CRT has a strong impact on health related quality of life (HRQoL): it was associated with changes in utility of [redacted] in NYHA I/II patients [redacted] in NYHA III/IV patients. There was also a small positive impact for ICD in patients with NYHA I/II [redacted], evidence of a quality of life benefit for ICD in NYHA III/IV is equivocal. Exploratory analysis of Minnesota Living with Heart Failure data showed that HRQoL benefits lasted for at least [redacted] years in all NYHA classes (contingent on being alive). A recently published paper arising from the CARE-HF study demonstrated significant CRT-P related HRQoL: benefits that were still apparent at study end (median follow up 2.5 years). In a more conservative approach than previous appraisals, we assumed that HRQoL benefits are maintained for five years and then taper off over time.

iii) All cause hospitalisation

A ‘number of events per month’ based approach was used. Amongst patients receiving OPT, NYHA class, ischemic aetiology status, QRS duration and age were all independent predictors of hospitalisations. Device therapy is associated with significant reductions in all cause monthly hospital admission rates across all NYHA classes. In NYHA class I to class III, ICD therapy reduced monthly admission rates by [redacted] and CRT by [redacted] The effect in NYHA class IV patients is even more pronounced, with CRT offering a [redacted] reduction in monthly admission rates.

Summary of findings from economic modelling

We used conservative assumptions throughout the economic modelling. In particular, in contrast to the models used in TA95 and TA120, we assumed that any treatment effects on mortality or HRQoL are not constant but diminish over time, with the ‘tailing off’ beginning after five years in our model. ICD and CRT device longevity is based on time to replacement data from approximately 40,000 UK implants provided by the Central Cardiac Audit Database (run by the NHS information Centre). Data were made available for approximately ten years of follow up. This is unique data on UK-only implants.

Implant costs were based on a combination of UK NHS specific average selling prices (aggregated across all manufacturers and device subtypes) and NHS tariff values. The aggregate data were supplied via the Association of British Healthcare Industries. The values used in the model for ICD, CRT-P and CRT-D implants (including hospital admission costs) are £15,248, £8,281 and £17,849 respectively.

Results of the base case deterministic cost-effectiveness analysis are presented fully incrementally for 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology. Data from 4,992 distinct patient profiles were aggregated to generate weighted lifetime costs and QALYs in these groups, with patient counts used to undertake all weightings. Thus, patient level heterogeneity has been fully incorporated into the economic evaluation. Ischemia did not significantly affect cost-effectiveness; the results presented below are therefore applicable to both ischemic and non-ischemic patients.

Base case results (all relate to patients with LVEF ≤35%)

NYHA I/II

For patients with a QRS < 120ms, the ICERs are below £25,200 per QALY gained and cost-effective; ICD is likely to be an acceptable use of resources. For patients with a QRS duration between 120 and 149ms and no LBBB, ICD is cost-effective with ICERs all approximately £17,000 per QALY gained. In patients with LBBB all ICERs for CRT-D are below £24,500 per QALY gained, meaning CRT-D is likely to be cost-effective. For patients with QRS ≥ 150ms, with or without LBBB: CRT-D is, overall, a cost-effective treatment (all ICERs less than £27,200 per QALY gained).

NYHA III

For patients with a QRS<120ms, the only intervention of interest is ICD and all ICERs are below £29,500 per QALY gained and cost-effective. For patients with QRS 120-149ms: CRT-P is cost-effective (all ICERs less than £19,700 in absence of LBBB and £15,500 in presence of LBBB). CRT-D generates ICERs between £23,000 and £27,400 per QALY gained relative to CRT-P, and provides significantly greater mortality reductions, so is cost-effective and an acceptable use of resources. For patients with QRS ≥150ms: CRT-P is cost-effective (all ICERS below £14,400). Compared to CRT-P, CRT-D generates ICERs close to

£25,000 per QALY gained in absence of LBBB and close to £29,000 per QALY gained in the presence of LBBB, and is an acceptable use of resources.

With the exception of one small patient group, ICD is either dominated or extended dominated regardless of QRS duration.

Due to the high risk of sudden cardiac death in patients who are in NYHA class III, and hence the perceived clinical need for defibrillation based therapy, we ran a comparison of defibrillation based therapies to no device therapy (i.e. CRT-D/ICD to OPT). In all but one instance, ICD therapy was dominated/ extended dominated and the highest ICER generated for CRT-D vs. OPT was approximately £22,400 per QALY gained. Where ICD was not dominated, the ICER for ICD vs. OPT was approximately £19,700 per QALY gained and for CRT-D vs. ICD £27,400 per QALY gained. Hence, defibrillation based therapy is cost-effective in NYHA class III.

NYHA IV

For patients with a QRS < 120ms no comparative analysis was possible in this patient group. For all other patients, compared to OPT, CRT-P represents value for money in NYHA IV patients: all ICERs are close to or below £25,000 per QALY gained and cost-effective, with ICERs decreasing as QRS duration increases. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

Sensitivity analyses

When we assumed constant treatment effects for mortality and HRQoL, across all QRS and LBBB categories, in patients who are NYHA I-III the highest ICER generated is approximately £24,600 per QALY gained for the comparison of ICD to OPT in patients with ischemic, non-LBBB NYHA III heart failure. All other ICERs on the frontier, for all relevant comparisons are lower with the most cost-effective ICER being below £20,000 per QALY gained in ten of the seventeen distinct groups for which results were generated. The general picture in patients who are NYHA IV remains unchanged.

When we viewed NYHA as a mortality treatment effect modifier across all QRS and LBBB categories, the highest ICER generated in patients who are NYHA III is approximately £26,700 per QALY gained for the comparison of ICD to OPT in patients with ischemic, non-LBBB NYHA III heart failure. All other ICERs on the

frontier, for all relevant comparisons are lower, with nine of the seventeen most cost-effective ICERs being below £20,000 per QALY gained

Additional sensitivity analyses surrounding device longevity, procedure costs, and short term adverse event rates were performed to explore alternative modelling assumptions and potential changes in the NHS. Most generated ICERs lower than, or similar to, the base case values, confirming that the base case results are conservative.

Comparison of results to those deemed acceptable in previous appraisals

We found that for CRT, ICERs were nearly always lower than in the previous appraisal (except in NYHA IV). In particular, the ICERs for CRT-D vs. CRT-P in NYHA class III are 30% to 50% lower than the accepted 2007 value. For ICD, given that EP testing was not included as a covariate, it was not possible to generate ICERs assuming no EP testing in patients where ICD is recommended (NYHA class I/II, LVEF ≤35% and QRS <150ms). In the nearest equivalent patient groups, the values generated in the current model are similar to those generated previously when EP testing was stipulated.

In general, ICER improvements are likely to be due to lower real-terms total implant costs, increased device longevity, better estimates of the impact of treatment on mortality and HRQoL, and the explicit exploration of patient level heterogeneity.

Implications for clinical practice

We are advised that, while NYHA Class, LVEF and QRS duration remain integral to clinical decision making, other tests, in particular electrophysiology (EP) tests as specified in the guidance arising from TA95, no longer reflect best clinical practice. Other tests included in the TA95 and TA120 guidance (non-sustained VT on Holter monitoring and a requirement for mechanical dyssynchrony) do not have a firm basis in the RCT evidence, and are not required to demonstrate cost-effectiveness. These supplementary tests do not appear in recent European guidelines. Recent clinical guidelines have highlighted the importance of LBBB as a decision criterion.

The aim of this analysis was to generate simple decision rules to allow cardiologists to provide any given patient with the most beneficial intervention that falls within cost-effectiveness boundaries. On the basis of our findings, these can

be summarised as follows:

For patients with LVEF ≤35% but without LBBB:

- NYHA class I/II:
  - QRS duration < 150ms: ICD should be used.
  - QRS duration ≥150ms, the patient should be given CRT-D.
- NYHA class III:
  - QRS duration <120ms ICD should be offered.
  - QRS duration ≥120ms, doctors should use either CRT-D or CRT-P, with CRT-D the preferred device because of the high incidence of SCD in this population (and hence clinical need for defibrillation therapy).
- NYHA class IV:
  - QRS durations ≥120ms CRT-P is the treatment of choice

For patients with LVEF ≤35% and LBBB:

- NYHA class I, II or III: CRT-D is the treatment choice.
- NYHA class IV: CRT-P is the preferred treatment.

Guidance based on our findings would result in an increase in device implantation rates. **However, growth in implant rates should be viewed in the context that current rates are still below the minimum levels suggested under current guidance**. In addition, there remains unacceptable geographical variation in device implantation rates between different cardiac networks in England and Wales, suggesting many eligible HF patients are not being offered device therapy.

Most importantly, the devices under consideration prolong life and bring symptomatic and quality of life benefits to patients in the proposed widened indications, as well as reducing the burden on NHS services through reduced hospitalisation rates. We show that the cost of giving patients access to these benefits would not exceed willingness to pay thresholds given the substantive health outcome benefits observed.

Contents

Executive summary **2**

Contents **11**

Table of tables **14**

Table of figures **19**

Table of abbreviations **22**

1 Background **25**

1.1 Heart failure: disease overview 27

1.2 Epidemiology 31

1.3 Burden of illness 32

1.4 Description and current application of relevant technologies 33

1.5 Current UK guidance on implantable cardiac devices in heart failure 36

1.6 Current Service Provision 40

1.7 Price of technologies under appraisal 42

1.8 Equity and equality 43

2 Statement of the decision problem **44**

2.1 Overview 44

2.2 End points of interest in assessing clinical efficacy 47

2.3 Presentation of cost-effectiveness results 48

3 Clinical effectiveness: systematic review of the literature **50**

3.1 Identification and assessment of studies 51

3.2 Studies identified by the review 54

3.3 Baseline patient characteristics 55

3.4 Results from mortality end points 73

3.5 Heart failure related hospitalisations 81

3.6 Other clinical end points 83

3.7 Health related quality of life 90

3.8 Device- and procedure-related adverse events 94

3.9 Long-term follow-up data on mortality 96

4 Analysis of individual patient level data 98

4.1 Introduction 100

4.2 Mortality 101

4.3 Overview of methods 102

4.4 Description of analyses 112

4.5 Results 117

4.6 Discussion of results 135

4.7 All cause hospitalisation 138

4.8 Health related quality of life 147

5 Assessment of cost-effectiveness 162

5.1 Description of modelling approach 162

5.2 Mortality 163

5.3 Event probabilities 163

5.4 Resource use 168

5.5 Costs 169

5.6 Health related quality of life 175

5.7 Other parameters 176

6 Results from the cost-effectiveness analysis 177

6.1 Base case deterministic analysis 180

6.2 Deterministic sensitivity analyses 194

6.3 Results presented by LVEF category 203

6.4 Probabilistic sensitivity analysis 203

6.5 Discussion of cost-effectiveness results 204

7 Financial implications to the NHS and other parties 212

7.1 Introduction 213

7.2 Implant rates arising from previous appraisals 214

7.3 Input values for current budget impact assessment 214

7.4 Results 220

7.5 Implications to other interested stakeholders 222

Table of tables

Table 1: The NYHA HF classification 28

Table 2 The ACC/AHA classification 29

Table 3: Major actions by device type. 36

Table 4: European and US guidelines on CRT-P and CRT-D in heart failure..... 39

Table 5 European and US guidelines on ICD in heart failure 40

Table 6: Rationale for excluding interventions from some subgroups 45

Table 7: Summary of treatments and randomisation in each trial 57

Table 8: Summary of patient crossover in all included studies 60

Table 9: Baseline patient characteristics by NYHA class and LVEF 64

Table 10: Baseline patient characteristics: demography and QRS Morphology . 67

Table 11: Characteristics by cardiac history (n (%)) 70

*Table 12: Effect of interventions on all-cause mortality** 75

*Table 13: Effect of interventions on sudden cardiac death** 78

*Table 14: Effect of intervention on death due to heart failure** 80

*Table 15: Effect of intervention on incidence of hospitalisation** 82

Table 16:NYHA class, mean (SD) value at 90 days 84

Table 17:NYHA at baseline and six months (mean, SD) 84

Table 18: Change in NYHA class, number of pts (%) at 6 months (CRT-P and OMT only) 84

Table 19: Change in NYHA class , number of pts. (%) (CRT-D and ICD only) ... 84

Table 20: Change in NYHA class, number of pts. (CRT-D and ICD only) 84

Table 21: Improvement at 6 months in NYHA class symptoms (%) 84

Table 22: Change in NYHA class - baseline and 6 months (median, 95% CI) ... 85

Table 23: Change in NYHA class - baseline and 6 months (mean, SD) 85

Table 24: Percentage of patients that worsened/improved NYHA at 12 months 85

Table 25: NYHA class distribution after one year of treatment (number of pts) .. 85

Table 26: Effect of intervention on change in LVEF 87

Table 27: Effect of intervention on incidence of VT/VF (n/N) 89

Table 28: Health related quality of life: EQ-5D instrument (mean (95% CI))..... 90

Table 29: Absolute MLWHF scores by study..... 92

*Table 30: Effect of intervention on change in MLWHF scores** 92

Table 31: Effect of intervention: change in MLWHF dimension scores (mean (SD)) 93

Table 32: Trials included in network meta-analysis - IPD availability..... 105

Table 33: Cross-over during follow-up provided for IPD Trials 106

Table 34: Follow-up period used in analysis of IPD Trials dataset 107

Table 35: Covariable data for IPD Trials dataset..... 110

Table 36: UK Summary data (reproduced from Cunningham et al., 2010) 111

Table 37: Preferred baseline risk model..... 121

Table 38: Results of univariate analysis and multivariate automated stepwise analyses used to inform interaction effect selection 129

Table 39: Preferred model for IPD network meta-analysis 132

Table 40: NBRM results used to predict all cause hospitalisation in OPT arm (baseline risk)..... 139

Table 41: Monthly probability of hospitalisation by covariate pattern (OPT) 140

Table 42: Negative binomial model used to predict the impact of treatment on all cause hospitalisations per month 142

Table 43: Derived all cause hospitalisation treatment effects..... 142

Table 44: All cause hospitalisation treatment effects used in the model (events per month)..... 143

Table 45: Monthly all cause hospitalisation transition probabilities (ICD, events per month)..... 144

Table 46: Monthly all cause hospitalisation transition probabilities (CRT-P, events per month) 144

Table 47: Monthly all cause hospitalisation transition probabilities (CRT-D, events per month) 145

Table 48: Overview HRQoL modelling approaches used in previous economic models 148

Table 49: Age and gender specific UK EQ-5D population norms (mean, SD.) reproduced from Kind et al. [134] 150

Table 50: Regression coefficients used to model age specific population utility 150

Table 51: Distribution of baseline EQ-5D observation counts by NYHA class .. 151

Table 52: NBRM Coefficients used to predict baseline utility decrement 152

Table 53: Comparison of indicative individuals with population equivalents (non-ischaemic aetiology) 153

Table 54: Comparison of indicative individuals with population equivalents (ischaemic aetiology) 153

Table 55: Summary EQ-5D statistics from the three clinical trials in which data was collected 154

Table 56: Mean changes from baseline in EQ-5D at six months by device and NYHA group (mean, s.e.) 155

Table 57: Mean changes from baseline in MLWHF at six months by device and NYHA group (mean, s.e.) 156

Table 58: Treatment specific utility increments used in the economic model ... 157

Table 59: CARE-HF based long term EQ-5D gains (mean, 95% CI) reproduced from Cleland et al. [56] 158

Table 60: Parameters used to derive time to second and subsequent device replacement estimates 167

Table 61: Distribution of reasons for hospitalisations by intervention 168

Table 62: Background medication by NYHA class 169

Table 63: Recommended doses 170

Table 64: Purchase costs 171

Table 65: Total cost of treatment per 1 month model cycle 172

Table 66: Hospitalisation event costs 173

Table 67: ICD and CRT system costs 174

Table 68: Device costs used in the model 175

Table 69: Remaining model parameters 176

Table 70: Deterministic base case results (patients without LBBB) 181

Table 71: Deterministic base case results (patients with LBBB) 182

Table 72: Deterministic base case results (NYHA III, CRT-D vs. OPT) 182

Table 73: Deterministic base case results (NYHA III, CRT-D vs. ICD vs. OPT) 184

Table 74: Deterministic sensitivity analysis – constant mortality treatment effect (no LBBB) 195

Table 75: Deterministic sensitivity analysis – constant mortality treatment effect (with LBBB) 195

Table 76: Deterministic sensitivity analysis – constant HRQoL treatment effect (no LBBB) 197

Table 77: Deterministic sensitivity analysis – constant HRQoL treatment effect (with LBBB) 197

Table 78: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (no LBBB) 198

Table 79: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (with LBBB) 199

Table 80: Deterministic sensitivity analysis –alternative all-cause mortality treatment effects (no LBBB) 200

Table 81: Deterministic sensitivity analysis – alternative all-cause mortality treatment effects (with LBBB) 201

Table 82: Deterministic sensitivity analysis – 10% increase in device longevity (no LBBB) 202

Table 83: Deterministic sensitivity analysis – 10% increase in device longevity (with LBBB) 202

Table 84: Summary of most cost-effective ICERs across all analyses (ischaemic individuals without LBBB) 206

Table 85: Summary of most cost-effective ICERs across all analyses (ischaemic individuals with LBBB) 207

Table 86: Summary of cost-effectiveness recommendations arising from our analysis* 208

Table 87: England and Wales population estimates (in millions) 2012-2016 215

Table 88: Projected ICD implant rates (per million) and procedure counts 216

Table 89: New implant counts (CRT-P and CRT-P) reproduced from the HES database 217

Table 90: Projected CRT implant rates (per million) and procedure counts 217

Table 91: Implant rates (per million) used in all alternative scenarios 218

Table 92: Annual cost of treatment estimates used in the financial impact assessment 219

Table 93: Survival estimates used in the financial impact assessment 220

Table 94: Budget impact analysis: Scenario one 220

Table 95: Budget impact analysis: Scenario two 220

Table 96: Budget impact analysis: Scenario three 221

Table 97: Budget impact analysis: Scenario four 221

Table of figures

Figure 1 Changing proportions of deaths from progressive HF and SCD by NYHA Class. SCD is the commonest cause of death in both NYHA II and NYHA III, while progressive HF is most important in NYHA IV. Data from MERIT-HF 31

Figure 2 Location of ICD and leads 34

Figure 3: Function and lead positioning of a dual chamber ICD 34

Figure 4: Lead positioning in a CRT device 35

Figure 5: New ICD implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010.[21] 41

Figure 6: New CRT (CRT-P and CRT-D combined) implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010.[21] 41

Figure 7: Observed ASPs for CRT-P and expected inflation-adjusted price (data on file, ABHI) 42

Figure 8: Observed ASPs for CRT-D and expected inflation-adjusted price (data on file, ABHI) 43

Figure 9: Observed ASPs for ICD and expected inflation-adjusted price (data on file, ABHI) 43

Figure 10: Example cost-effectiveness plane 48

Figure 11: Illustration of dominance and extended dominance 49

Figure 12: Network of randomised controlled trials 103

Figure 13: Comparison of Kaplan Meier and parametric curves for patients in different risk quintiles (risk quintiles defined by the parametric model) 119

Figure 14: Predictions over 50 year time horizon (by risk quintiles) 120

Figure 15: Example predictions, with and without age as time-dependent covariable: low risk patient (male, age 51 in NYHA class I/II, non-Ischaemic aetiology, QRS duration <120ms and LVEF between 25% and 30%) 122

Figure 16: Example predictions, with and without age as time-dependent

covariable: high risk patient (male, age 71 in NYHA class III, ischaemic aetiology, QRS duration>120ms and LVEF ≤20%)..... 122

Figure 17: Comparison of network meta-analysis results using IPD Trials and All Trials, and fixed and random effects models 124

Figure 18: Comparison of Fixed Effects IPD Trials analysis to individual trial results 125

Figure 19: Forest plot of results of analysis adjusting for covariables (LBBB) .. 133

Figure 20: Comparison of observed vs. fitted baseline hospitalisation rates (events per month) 140

Figure 21: Histogram of baseline EQ-5D data across all three clinical trials..... 151

Figure 22: Histogram of baseline EQ-5D data across all three clinical trials expressed as proportional change from unity..... 151

Figure 23: difference in difference (device-OPT) long term change in MLWHF (NYHA I/II)..... 159

Figure 24: difference in difference (device-OPT) long term change in MLWHF (NYHA III)..... 159

Figure 25: UK device longevity data (Jan 2000 to April 2011, time unit: days) . 164

Figure 26: Parametric function fitted to UK CRT-P implant data..... 165

Figure 27: Parametric function fitted to UK ICD implant data 165

Figure 28: Parametric function fitted to UK CRT-D implant data 166

Figure 29: Extrapolation of parametric functions: CRT-D data only..... 166

Figure 30: CE frontier (NYHA II, ischaemic aetiology, no LBBB)..... 186

Figure 31: CE frontier (NYHA II, ischaemic aetiology, LBBB)..... 187

Figure 32: CE frontier (NYHA II, ischaemic aetiology, LBBB)..... 188

Figure 33: CE frontier (NYHA III, ischaemic aetiology, non-LBBB)..... 189

Figure 34: Cost-effectiveness frontier (NYHA III, ischaemic aetiology, with LBBB) 189

Figure 35: CE frontier (NYHA IV, ischaemic aetiology, LBBB, QRS>150ms)... 192

Figure 36: England and Wales annual ICD implant rates (Data taken from

Cunningham et al.) 215

Figure 37: England and Wales annual CRT implant rates (Data taken from Cunningham et al.) 216

Table of abbreviations

Abbreviation	Full description
2LL	Two times log-likelihood score
ABHI	Association of British Healthcare Industries
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Akaike's Information Criterion
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ARVD	Arrhythmogenic Right Ventricular Dysplasia
ASP	Average selling prices
AT/AF	Atrial tachyarrhythmia
BGR	Brooks Gelman-Rubin
BIC	Bayesian Information Criteria
BNF	British National Formulary
BNP	B-type natriuretic peptide
CCAD	Central Cardiac Audit Database
CENTRAL	Cochrane Central Register of Controlled Trials
CMT	Conventional medical therapy
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy defibrillator
CRT-P	Cardiac resynchronisation therapy pacemaker
DIC	Deviance information criteria

ECG	Electrocardiography
EF	Ejection fraction
EP	Electrophysiology
ESC	European Society of Cardiology
HES	Health Episode Statistics
HF	Heart failure
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health related quality of life
HRUK	Heart rhythm UK
ICD	Implantable cardioverter defibrillators
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention-to-treat
LBBB	Left bundle branch block
LOS	Length of stay
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MLWHF	Minnesota Living with Heart Failure Questionnaire
ms	millisecond
NBRM	Negative binomial regression
NYHA	New York Heart Association
OMT	Optimal medical therapy
OPT	Optimal pharmacological therapy

OS	Overall survival
PASA	Purchase and Supplies Agency
PbR	Payment by results
PRM	Poisson regression
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SE	Standard error
SAE	Serious adverse event
SCD	Sudden cardiac death
SD	Standard deviation
SRC	Schedule of Reference Costs
Std. Dev	Standard deviation
VT/VF	Ventricular tachycardia/ ventricular fibrillation
ZINB	Zero Inflated Negative Binomial

1 Background

- Heart Failure (HF) is a clinical syndrome characterised by breathlessness, fatigue and fluid retention. It is classified using New York Heart Association (NYHA) functional class, ranging from Class I (no limitation of physical activity) to Class IV (symptomatic at rest and discomfort from any physical activity).
- Age-adjusted prevalence of diagnosed HF in the UK is approximately 0.9% (men) and 0.7% (women).
- Heart failure is a major cause of mortality and morbidity. It accounts for approximately 1 million inpatient bed days annually (2% of all NHS inpatient days), and 5% of medical emergency hospital admissions.
- Prognosis is poor despite optimal pharmacological therapy. Implantable devices have an established role in these treatment of patients.
- HF-related mortality results from sudden cardiac death due to ventricular arrhythmias (most common in NYHA I to III) or progressive HF (most common in NYHA IV).
- Patients with structural heart disease which does not result in heart failure as well as patients with primary conditions are also at risk of sudden cardiac death.
- The implantable cardioverter defibrillator (ICD) continuously monitors the heart for arrhythmia and maintains normal heart rate using painless electrical stimulation. In the event of a potentially life-threatening arrhythmia it can deliver rapid stimulation or an electrical shock (defibrillation).
- Cardiac resynchronisation therapy (CRT) is a form of pacing that uses electrical stimulation to resynchronise the contraction of the ventricles, thereby improving pumping efficiency.

- Devices that deliver CRT alone are known as CRT-P. Devices which combine CRT with a defibrillation function, offering protection from sudden cardiac death in addition to the benefits of CRT are known as CRT defibrillators (CRT-D)
- New evidence has become available and UK clinical practice has evolved since current UK guidance on ICDs and CRT was published in 2006/2007. In addition, device costs have fallen in real terms. Further, as with many similar technologies there has been a reduction in procedural invasiveness and procedural efficiency. Thus, both clinical recommendations and cost-effectiveness calculations will need to be re-examined in the light of current data.
- While NYHA Class, LVEF and QRS duration remain integral to decision making for ICD and/or CRT therapy, other tests for example electrophysiology (EP) tests included in TA95 guidance have been shown to have limited sensitivity and specificity and no longer reflect best clinical practice.
- Device implantation rates vary considerably between cardiac networks within England and Wales: The adjusted annual number of new ICD implants per million population varied from 34 to 131, and implantation rates for new and replacement CRT devices ranged from 68 to 182/million.
- The Network Device Survey Group and Heart Rhythm UK have suggested a minimum annual target of 100 new ICD implants/million population and 130 total (new + replacement)/million for CRT (CRT-P and CRT-D combined). Current rates in England are approximately 72/million and 114/million, respectively, suggesting continuing under-provision.
- Device prices paid by the NHS have either remained constant or declined over the five years from 2006-2010. In real terms, after adjustment for inflation, average prices have fallen by 17% for CRT-P, 10% for CRT-D and 8% for ICD.

1.1 Heart failure: disease overview

1.1.1 Definition

Heart failure (HF) can be defined as ‘A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood’.[1;2] Because not all patients have volume overload, the older term ‘congestive heart failure’ is no longer preferred.

The most common cause of HF is myocardial dysfunction, commonly left ventricular systolic dysfunction, which reduces mechanical efficiency and can also lead to dysynchronised pumping. Myocardial dysfunction is most often caused by damage to heart muscle. In western countries, coronary artery disease is the initiating cause in about 70% of cases of HF. A further 10% of cases arise from valve dysfunction and 20% from non-ischaemic cardiomyopathies, with perhaps half of those being ‘idiopathic’ [no known cause].[3]

Whatever the precipitating event, a complex and wide-ranging set of adaptive mechanisms comes in to play to compensate for the underlying dysfunction. Although these initially enable adequate cardiac function to be maintained, over time they contribute to a vicious cycle in which pathological remodelling of the heart leads to further deterioration in cardiac function. As well as affecting mechanical function, these changes can also lead to electrical instability.[4]

HF is a clinical diagnosis based on physical examination and patient history; there is no specific diagnostic test. Additional evaluation may include exercise testing, echocardiography or cardiac catheterisation and blood testing. The most recent NICE guidance recommends that a patient with suspected heart failure (due to symptoms, signs, and history) should have a BNP blood test and be fully assessed by a specialist within two to six weeks.[5]

1.1.2 Symptoms

Symptoms are caused by an inability of the heart’s pumping capacity to support metabolic demands. Thus early-stage HF may produce symptoms only under conditions of high demand, principally exercise, whereas severe HF is symptomatic even at rest.

The characteristic symptoms of HF are breathlessness (dyspnoea), fatigue, and

fluid retention (oedema). The relative importance of breathlessness and fluid retention varies between patients. Other symptoms can include orthopnoea (breathlessness when lying down that is relieved by moving to a more upright position); paroxysmal nocturnal dyspnoea (breathless attacks at night); palpitations; nocturia; anorexia, nausea and weight loss; abdominal bloating and discomfort; confusion, light-headedness, and impaired memory.

1.1.3 Classification

The most widely used classification system for HF is the New York Heart Association (NYHA) classification, which is based on functional classes (see Table 1).

Table 1: The NYHA HF classification

NYHA Class	Definition
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnoea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

NYHA class can fluctuate over time. It is also prone to considerable inter-observer variability, and may not reflect important changes in exercise capacity.[2] Another limitation of the NYHA classification is that the severity of symptoms does not necessarily correlate with the severity of the underlying damage to the heart. Patients with severe damage can have relatively mild symptoms, and vice versa. Nevertheless, NYHA class has been shown in multiple clinical trials and observational studies to be an excellent predictor of morbidity and mortality in heart failure.

To complement the NYHA Classification, a staging system based on structural abnormality was developed by the American College of Cardiology and American Heart Association (the ACC/AHA classification; see Table 2). Stages A and B cover patients at high risk of developing HF, while patients with symptomatic HF are classed as stage C or D.

Table 2 The ACC/AHA classification

ACC/AHA Stage	Definition
A	Risk factors for HF (hypertension, diabetes) but otherwise no structural damage or symptoms.
B	Structural damage present (myocardial infarction, valvular disease, low ejection fraction) but no symptoms present
C	Structural heart disease with HF symptoms
D	Refractory, end-stage disease. Marked symptoms at rest despite maximal medical therapy

In practice, the terms mild, moderate, and severe are often used to describe NYHA Classes II, III, and IV, respectively.

1.1.4 Management

The goals of treatment in patients with established HF are to relieve symptoms and signs, prevent hospital admission, and improve survival.[4] Reductions in mortality and hospital admission rates reflect the ability of effective treatments to slow or prevent progressive worsening of HF. This is often accompanied by reversal of harmful cardiac remodelling. Effective therapies also improve functional capacity and quality of life.[4]

The cornerstones of medical therapy are diuretics, ACE inhibitors and beta-blockers, with the addition of a mineralocorticoid receptor antagonist and/or digoxin if this triad is not sufficiently effective.[4] Implantable devices are used in the treatment of patients who remain symptomatic despite optimal medical therapy (see 1.4). Ventricular assist devices and transplantation are options for selected patients in end-stage HF.[4]

1.1.5 Prognosis

Even with the use of optimal pharmacological therapy, the prognosis for HF is poor. UK studies show one-year mortality from diagnosis for all-class HF is just under 40%.[6;7] About half of patients will die within 4 years.[3] There are two mechanisms of HF-related death: progressive HF (failure of the heart's ability to pump), and sudden cardiac death (SCD; see section 1.1.6), most commonly defined as death from a cardiovascular cause within one hour of the onset of symptoms. SCD is the most common cause of HF-related death in mild to moderate HF, while progressive HF failure is more common in severe HF (Figure

1).

Role of left bundle branch block

Patients with HF often have electrical dysfunction of the heart resulting in delayed activation and contraction of areas of the myocardium, leading to cardiac dyssynchrony.[8] The most common conduction abnormality is left bundle branch block (LBBB) which delays conduction to the left ventricle and affects approximately one-third of patients with chronic stable HF.[9] An additional 11% will develop new-onset LBBB within one year of follow-up.

LBBB in the presence of HF has an adverse effect on haemodynamics and has been shown to be an independent predictor of decreased survival in an Italian study of patients with all forms of chronic heart failure published in 2002.[10] However, caution needs to be taken when interpreting the results from this study since, while multivariate, the authors did not control for QRS duration. Hence, the direct applicability of the results to the population being assessed in this appraisal is debatable. There is evidence that HF patients with LBBB (particularly those with mildly symptomatic disease) may derive an increased survival benefit from cardiac resynchronisation therapy,[11;12] which acts to reduce dyssynchrony. Hence, CRT may be a treatment effect modifier in patients with LBBB.

Role of atrial fibrillation

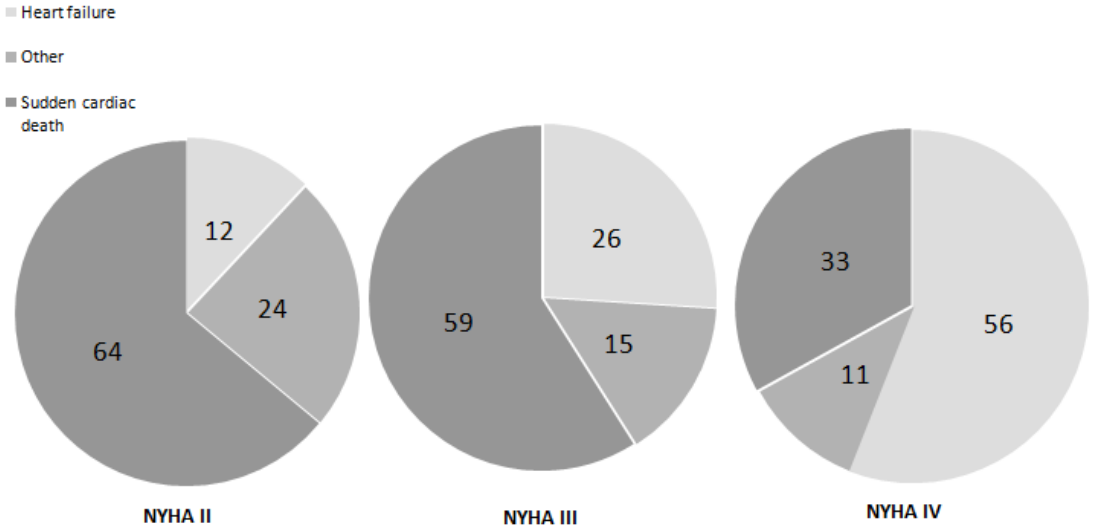
Most of the randomised controlled trials of CRT have excluded patients with persistent atrial fibrillation (AF), although those with paroxysmal AF were often included. AF can reduce the effect of CRT by reducing the proportion of biventricular pacing, and this has been associated with poorer outcomes.[13] However, when at least 95% biventricular pacing is achieved by increasing atrio-ventricular block with medical or ablation therapy, similar beneficial effects are seen in patients in AF and sinus rhythm. AF is not considered a contraindication to CRT in clinical practice. The European Society of Cardiology (ESC) estimates that 20% of CRT implantations in HF are in patients with AF[3] and both ESC and American guidelines endorse the use of CRT in patients with AF (see Section 1.5), provided adequate rate control can be achieved by either drugs or atrioventricular node ablation.

1.1.6 Sudden cardiac death in HF

Sudden cardiac death (SCD) is generally defined as a natural death resulting from cardiac causes in a person with or without pre-existing heart disease, within 1 hour of onset of acute symptoms.[14] In 75% of SCDs the underlying disease is coronary artery disease[15;16], and the risk factors with the highest predictive value for SCD are reduced left ventricular ejection fraction and clinical HF.[17;18]

SCD is the most common cause of death for HF patients in NYHA classes I, II, and III, accounting for 64% and 59% of on-study deaths, respectively, in the MERIT-HF study (Figure 1).[19] In severe HF, the largest proportion of deaths (56% in MERIT-HF) are from progressive HF, although SCD still accounts for approximately one-third.

Figure 1 Changing proportions of deaths from progressive HF and SCD by NYHA Class. SCD is the commonest cause of death in both NYHA II and NYHA III, while progressive HF is most important in NYHA IV. Data from MERIT-HF



1.2 Epidemiology

1.2.1 Incidence and prevalence

The age-standardised incidence of HF in England (2009) is approximately 37.5/100,000 for men and 23/100,000 for women.[20] The incidence rises steadily with age, increasing in men from 19.2/100,000 at age 45-54 to 72.3 at age 55-64, 179.3 at age 65-74 and 326.0 at age 75+. In women, the equivalent incidence

rates are 9.1, 31.7, 102.9 and 256.2, respectively. In the UK, the mean ages of ICD, CRT-D and CRT-P implant are 63.1, 67.1 and 71.7 years respectively.[21] these values are in line with patients recruited into major clinical trials (see section three) meaning that they were conducted in patients of comparable age to the UK HF population. A commonly quoted study of UK heart failure patients reported an incidence of approximately 1:1000 per annum which would result in approximately 65,000 new cases of HF in the UK each year.[22]

Age-adjusted prevalence of diagnosed HF in England in 2009 was 0.9% for men and 0.7% for women.[20] Prevalence is highest in people aged 75 or over, at 13.7% in men and 12.5% in women. Prevalence of HF in an English population-based study was found to be approximately 1 in 35 people aged 65–74 years, rising to approximately 1 in 15 at age 75–84, and more than 1 in 7 at age 85 and older.[23] In the UK Heart of England study, 31% of definite HF patients were found to have class NYHA III and IV symptoms.[23]

The incidence and prevalence of HF are likely to increase, due to ageing of the population and therapeutic advances in the management of acute myocardial infarction and other cardiovascular conditions.[23] Increasing numbers of people are surviving acute myocardial infarction but are left with permanent left ventricular dysfunction, and are consequently at high risk of developing HF.[24]

1.3 Burden of illness

1.3.1 Economic cost

Heart failure is a major cause of mortality and morbidity in the UK and is responsible for about 2% of total NHS spending.[25] It accounts for approximately one million inpatient bed days annually (2% of all NHS inpatient days), and 5% of medical emergency hospital admissions.[26] One patient in four is readmitted within three months of HF hospitalisation.[27] It is projected that admissions due to HF will increase by 50% in the 25 years from 2010.[26]

Hospitalisation accounts for 60-70% of the healthcare cost of HF. The costs extend beyond direct healthcare costs associated with the initial admission. Stewart et al. estimated that secondary HF admissions and long term nursing care consumed an additional 2% of UK healthcare expenditure.[28] A recent study has generated similar findings.[29]

1.3.2 Humanistic burden

Quality of life is affected both by the physical limitations resulting from HF and by the consequent limitations on social activity. This in turn can affect psychological and emotional wellbeing. In people with severe HF, functional ability is severely limited and depression is common.[30]

HF has been shown to have an important impact on all aspects of quality of life, in particular patients' mobility and usual activities.[31] For example, patients with HF in the CARE-HF study were found to have significant HRQoL reductions (as measured using the EQ-5D instrument) compared with a representative sample of the UK population. The authors concluded that the impact of HF varies amongst patients, but the overall burden of disease appears to be comparable to other chronic conditions such as motor-neuron disease or Parkinson's disease.

1.4 Description and current application of relevant technologies

A range of devices is available from different manufacturers. These differ in their specifications and features: Manufacturers' literature should be consulted for product-specific information. The principal characteristics of the three technology classes under assessment are described below.

1.4.1 Implantable cardioverter defibrillator (ICD)

An implantable cardioverter defibrillator (henceforth "ICD") is a small, battery powered device that is implanted under the skin (often sited below the collar bone; Figure 2). It continuously monitors the heart for arrhythmia (ventricular tachyarrhythmia/ventricular fibrillation) and, depending on its programming, acts to restore normal heart rate using small, painless electrical signals. If necessary the device delivers a stronger shock (defibrillation) that is triggered when it senses a potentially life-threatening arrhythmia.

An ICD system typically includes three parts: the ICD itself, leads and a programmer. The leads are implanted as shown in Figure 3, and carry signals between the ICD and the heart. Dual chamber (atrial and ventricular sensing and pacing) and single chamber (ventricular sensing and pacing only) devices are available. The programmer is in an external computer located in a doctor's office or clinic. Many ICD systems now include remote monitoring: A device installed in the patient's home transmits data from the ICD to a secure website where it can

be viewed by the clinical team. This alerts the team to any significant events and minimises the need for patients to travel to hospital for device review. The ICD can be programmed in order to optimise the detection and treatment of arrhythmias and provide diagnostic information important to patient management.

Figure 2 Location of ICD and leads

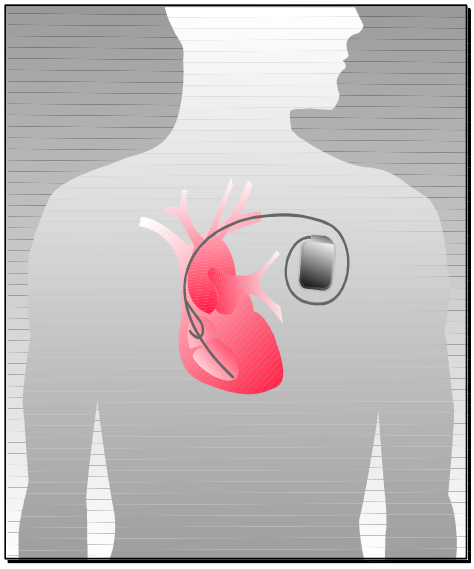
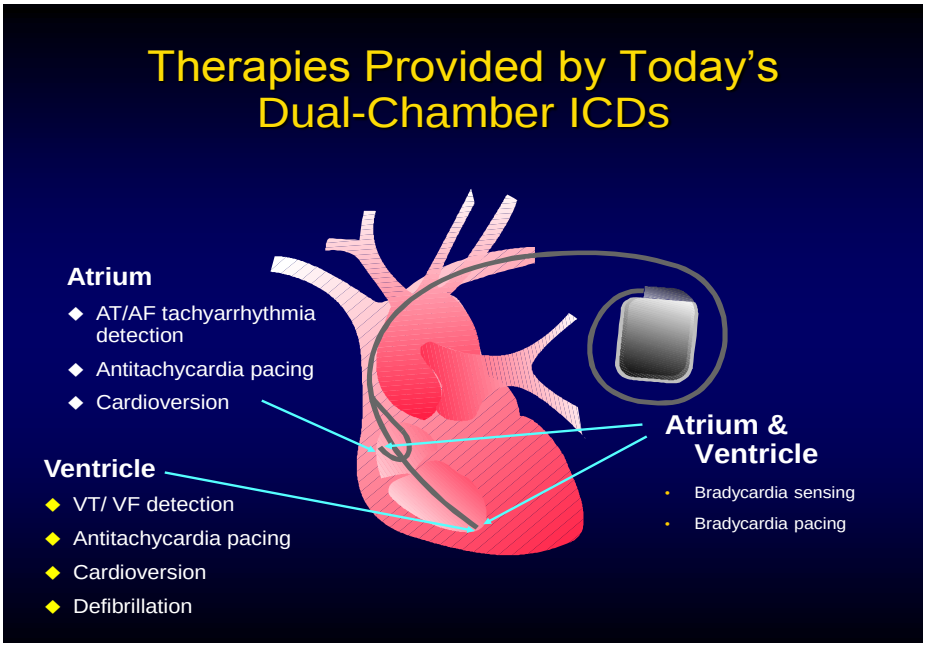


Figure 3: Function and lead positioning of a dual chamber ICD



1.4.2 Cardiac resynchronisation therapy (CRT)

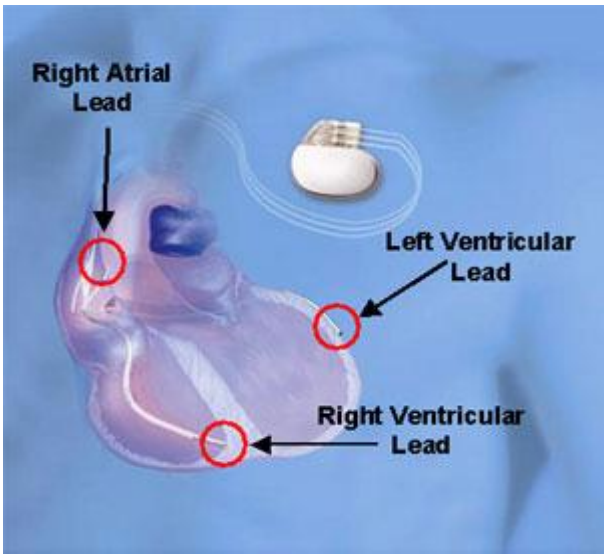
CRT-P

Cardiac resynchronisation therapy (CRT), also known as biventricular pacing, uses an implantable device to deliver pacing via biventricular or left ventricular electrical stimulation. For HF patients with impaired electrical conduction in the heart, CRT is intended to resynchronise the contraction of the ventricles, thereby improving pumping efficiency and increasing blood flow to the body. This may reduce HF symptoms, improve quality of life and increase patients' ability to perform the tasks of daily living. CRT is intended to complement standard drug therapy, dietary and lifestyle modifications.

CRT involves implantation of a pulse generator in the upper chest of the pulse generator, from which three leads descend via veins into the heart. Leads are placed in the right atrium and the right ventricle, with a third lead (the left ventricular lead) usually being placed in the coronary sinus (Figure 4). Implantation success rates in clinical trials have been high. For example, the success rate in the CARE-HF study was 96%.[32]

CRT with pacing function only, as described above, is henceforth referred to as "CRT-P".

Figure 4: Lead positioning in a CRT device



CRT-D

HF patients are also at risk of sudden cardiac death and may benefit from an implantable cardioverter defibrillator, or a combination CRT/defibrillator

(henceforth “CRT-D”). CRT-D is designed to combine the distinct but complementary benefits of CRT and ICD devices.

1.4.3 Summary of device actions

A summary of the major actions of each device type is presented in Table 3 below. Of note, CRT-P does not offer defibrillation in the event of potentially fatal arrhythmia, so does not directly protect against SCD.

Table 3: Major actions by device type.

Action	ICD	CRT-P	CRT-D
Heart rate (bradycardia) pacing	✓	✓	✓
Cardiac resynchronisation (improves pumping efficiency)	x	✓	✓
Arrhythmia detection and correction (anti-tachycardia pacing, cardioversion and defibrillation to prevent SCD)	✓	x	✓

✓ - Performs function; x - does not perform function

1.5 Current UK guidance on implantable cardiac devices in heart failure

Implantable cardiac devices in HF are addressed by NICE Technology Appraisals 95 (ICD, henceforth ‘TA95’)[33] and 120 (CRT-P and CRT-D, henceforth ‘TA120’)[34]. The NICE Guideline on Heart Failure (CG 108, 2010)[5] refers to these two appraisals and does not provide new recommendations.

1.5.1 CRT-P and CRT-D

Under NICE guidance issued in 2007 (TA120[35]), CRT-P is recommended as a treatment option for people with HF who fulfil all the following criteria:

- They are currently experiencing or have recently experienced NYHA class III–IV symptoms
- They are in sinus rhythm: **either** with a QRS duration of 150ms or longer estimated by standard ECG; **or** with a QRS duration of 120–149ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography
- They have a left ventricular ejection fraction of 35% or less

- They are receiving optimal pharmacological therapy.

CRT-D may be considered for people who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD device, as recommended in TA95 (see section 1.5.2 below).

1.5.2 ICD

NICE guidance issued in 2006 (TA95[36]) recommends ICDs for the following categories of patient:

'Secondary prevention', that is, for patients who present, in the absence of a reversible cause, with one of the following:

- Having survived a cardiac arrest due to either VT or VF
- Spontaneous sustained VT causing syncope or significant hemodynamic compromise
- Sustained VT without syncope or cardiac arrest, and who have an associated reduction in EF (LVEF < 35%) (no worse than NYHA III)

'Primary prevention', that is, for patients who have:

- A history of previous (> 4 weeks) myocardial infarction (MI) and: either

  LV dysfunction with LVEF <35% (no worse than NYHA III), **and** non-sustained VT on Holter (24-hour ECG) monitoring, **and** inducible VT on EP testing;

  or

  LV dysfunction with an LVEF <30% (no worse than NYHA III) **and** QRS duration of equal to or more than 120ms.
- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, ARVD, or have undergone surgical repair of congenital heart disease.

TA95 does not cover the use of implantable defibrillators for non-ischaemic dilated cardiomyopathy.

1.5.3 Discussion of current guidance

Current NICE guidance is based on the clinical evidence available up to its

publication in 2006/2007. Since then, the evidence base has expanded, and UK clinical practice has evolved. In addition, device costs have fallen by 9-17% in real terms (see Section 1.7). Thus, it is to be expected that both clinical recommendations and cost-effectiveness calculations will need to be re-examined in the light of current data.

Several major trials have been published since the previous guidance, notably

- SCD-HeFT
- MADIT-CRT
- RAFT
- REVERSE

SCD-HeFT examined the use of ICDs in NYHA II and III patients, the remaining trials focus primarily on the use of CRT-D versus ICD in patients who are mild to moderately symptomatic (NYHA I/II) and are discussed in detail in Section three of the dossier. In terms of UK clinical practice, we have sought expert opinion on changes since the last guidance. We are advised that, while NYHA Class, LVEF and QRS interval remain integral to decision making, other tests, in particular electrophysiology (EP) tests as specified in the guidance arising from TA95, no longer reflect best practice.

The most recently updated international guideline was issued by the European Society of Cardiology in May 2012. Its recommendations are summarised in Table 4 and Table 5, along with the most recent US guidelines dating from 2008. All recommendations apply to patients who are receiving optimal medical therapy and have expected survival with good functional status of more than one year.

Table 4: European and US guidelines on CRT-P and CRT-D in heart failure.

Patient population	Recommendation	Level
European Society of Cardiology (2012)[4]		
NYHA Class II		
LBBB QRS morphology		
LVEF ≤30%, QRS ≥130 ms, sinus rhythm	CRT, preferably CRT-D, is recommended to reduce risk of HF hospitalisation and risk of premature death	IA
Non- LBBB QRS morphology LVEF ≤30%, QRS ≥150 irrespective of morphology, sinus rhythm	CRT, preferably CRT-D, should be considered to reduce risk of HF hospitalisation and risk of premature death	IIaA
NYHA Class III/IV		
LBBB QRS morphology		
LVEF ≤35%, QRS ≥120 ms, sinus rhythm, ambulant	CRT-P/CRT-D is recommended to reduce risk of HF hospitalisation and risk of premature death	IA
Non-LBBB QRS morphology		
LVEF ≤35%, QRS ≥150 ms irrespective of morphology, sinus rhythm, ambulant	CRT-P/CRT-D should be considered to reduce risk of HF hospitalisation and risk of premature death	IIaA
Permanent AF		
LVEF ≤35%, QRS ≥120 ms, ambulant	CRT-P/CRT-D may be considered to reduce risk of HF worsening if: pt requires pacing for intrinsically slow ventricular rate; or is pacemaker-dependent resulting from AV nodal ablation; or has ventricular rate≤ 60 bpm at rest and ≤ 90 bpm on exercise	IIbC
American Heart Association/American College of Cardiology (2008)[2]		
NYHA Class III/IV		
LVEF ≤35%, cardiac dyssynchrony (QRS ≥120 ms), sinus rhythm, ambulant	Should receive cardiac resynchronisation therapy, with or without ICD, unless contraindicated	IA
LVEF ≤35%, QRS ≥120 ms, atrial fibrillation, optimal medical therapy, ambulant	CRT with or without an ICD is reasonable	IIaB

Table 5 European and US guidelines on ICD in heart failure

Patient population	Recommendation	Level
European Society of Cardiology, 2012[4]		
NYHA Class II/III		
LVEF ≤ 35%, optimal medical therapy	ICD is recommended for primary prevention of sudden cardiac death	IA (ischaemic aetiology)
i) Ischaemic aetiology≥ 40 days post-MI		IB (non-ischaemic aetiology)
ii) Non-ischaemic aetiology		
American Heart Association/American College of Cardiology[2]		
NYHA Class II/III		
As above, ischaemic or non-ischaemic aetiology	ICD is recommended for primary prevention of sudden cardiac death, to reduce total mortality	IA

1.6 Current Service Provision

There is significant local variation in ICD and CRT implantation rates within England and Wales. The 2010 UK National Clinical Audit on Cardiac Rhythm Management found that the adjusted annual number of new ICD implants per million population varied from 34 in the Cardiac Network with the lowest provision to 131 in the network with highest provision. Implantation rates for new and replacement CRT devices ranged from 68 to 182/million.[21]

The Network Device Survey Group, in its UK National Clinical Audit of Heart Rhythm Devices, states that, while targets remain open to investigation and debate, “realistic target implant rates, based on a consensus of the best epidemiological and international comparative data possible, serve as a vital stimulus for the planning and improvement of device services”.[21] The audit group uses an annual target of 100 new implants/million population for ICD and 130 total (new + replacement)/million for CRT (CRT-P and CRT-D combined). Current rates in England are approximately 72/million and 114/million, respectively, suggesting considerable under-provision of this treatment.[21] Figure 5 and Figure 6 show wide regional variation relative to these targets.

In addition, comparison of the ICD prevalence estimates presented in section 1.2 with the information in Figure 5 highlights the fact that the upper control limit on

current procedures is below the derives estimates for most network population sizes.

Figure 5: New ICD implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010.[21]

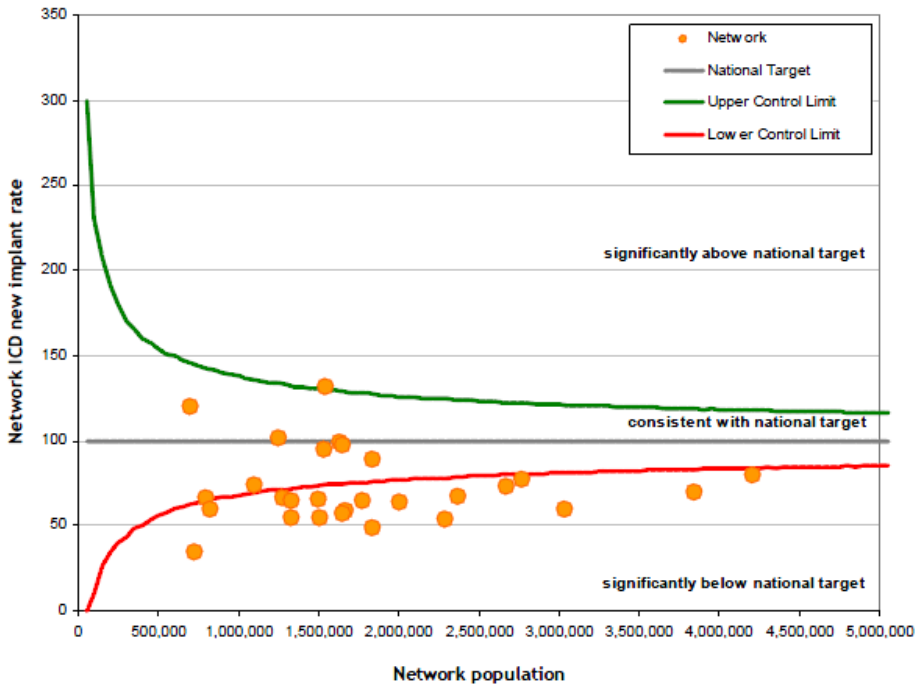
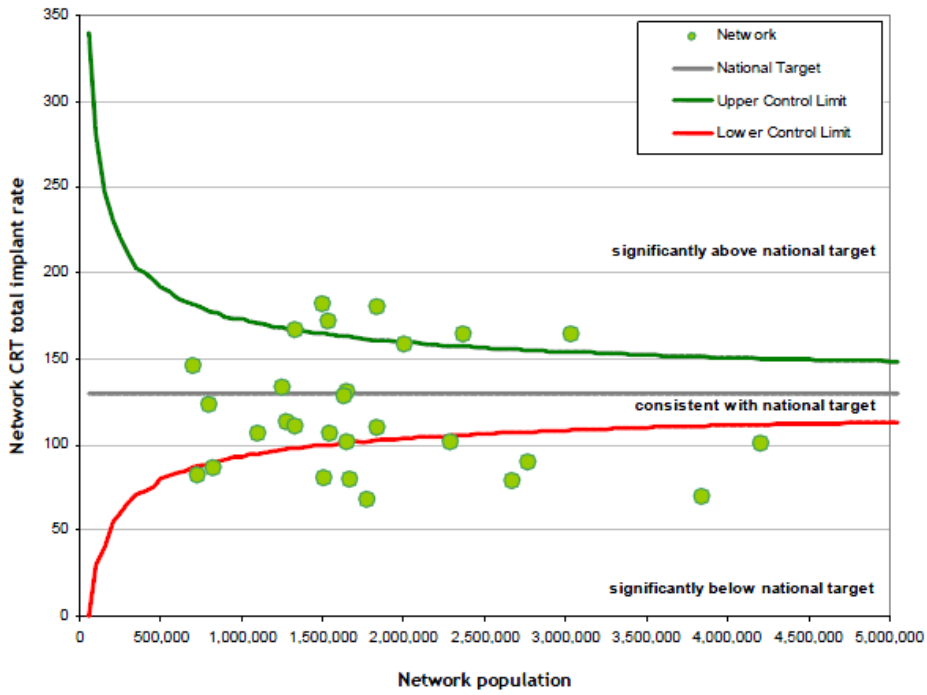


Figure 6: New CRT (CRT-P and CRT-D combined) implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010.[21]



1.7 Price of technologies under appraisal

UK NHS specific average selling prices (ASP) for both whole systems (devices and leads) and just leads were provided by five device manufacturers (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical) for all ICD and CRT devices from 2006 to 2011 inclusive via the Association of British Healthcare Industries (ABHI). These prices represent the actual costs paid in the UK NHS for CRT and ICD based treatments. 2006 data were not available for ICD therapy.

In order to make a fair comparison across years, the 2006 (CRT) and 2007 (ICD) values were inflated to 2011 equivalents (the most recent date of data availability) using the Hospital & Community Health Services pay inflation index.[37] The observed values are presented graphically in Figure 7 to Figure 9, along with the values expected if prices had risen in line with inflation. For all three treatment options, actual prices have declined over the five year period. In real terms, prices have fallen by 17% for CRT-P, 10.4% for CRT-D and 8% for ICD. When interpreting these values, it is impossible to know the impact of future innovation etc. on future prices. Hence, any trend in real term prices have not been extrapolated beyond the observed period.

Figure 7: Observed ASPs for CRT-P and expected inflation-adjusted price (data on file, ABHI)

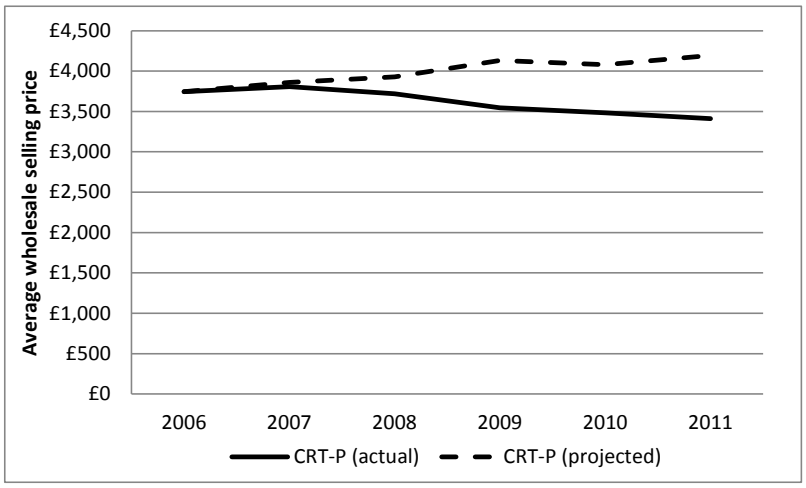


Figure 8: Observed ASPs for CRT-D and expected inflation-adjusted price (data on file, ABHI)

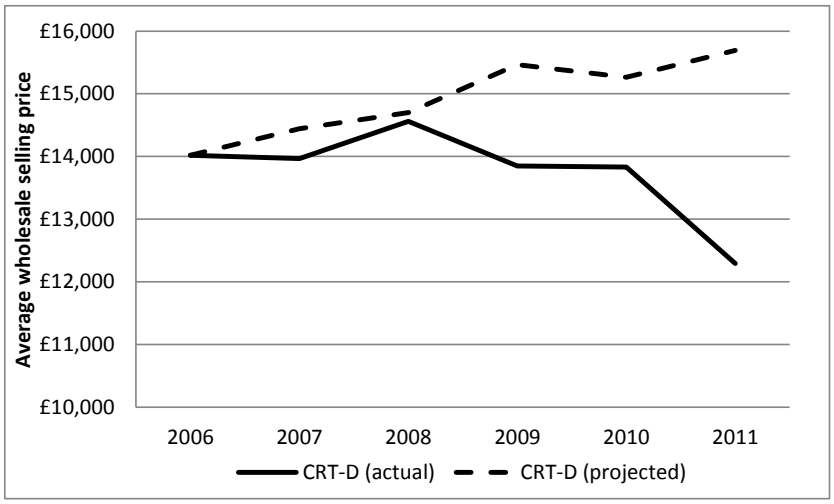
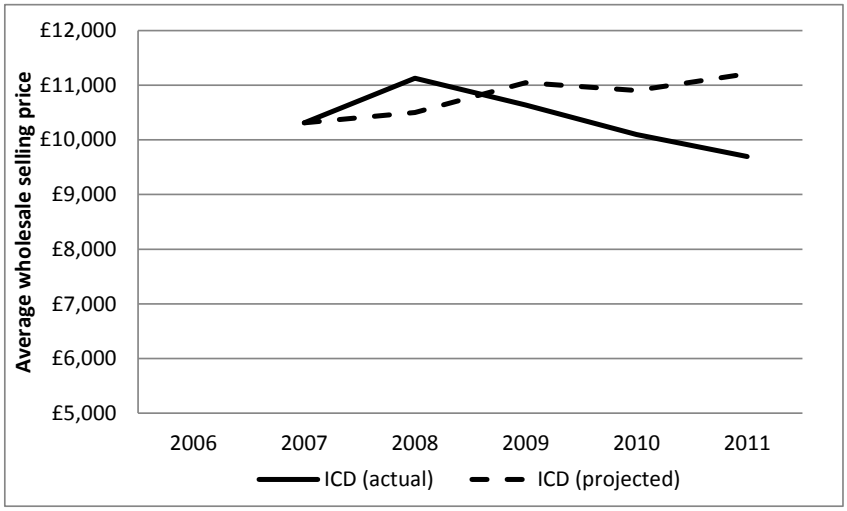


Figure 9: Observed ASPs for ICD and expected inflation-adjusted price (data on file, ABHI)



1.8 Equity and equality

1.8.1 Geographical

Device implantation rates vary widely between different regions of the UK (as defined by Cardiac Networks): see Section 1.6 for details. According to the National Director for Heart Disease, Roger Boyle, quoted in the 2010 HRUK Clinical Audit [21] this represents “a continuing and unyielding problem of geographical inequity of service provision” for ICD and CRT devices in the NHS. The report states that the causes of this inequity are not known.

2 Statement of the decision problem

2.1 Overview

2.1.1 Definition of the decision problem

The decision problems addressed in this submission are in line with the NICE scope, namely:

- Based on a range of commonly collected clinical parameters, who should receive an ICD device?
- Based on a range of commonly collected clinical parameters, who should receive a CRT-P device?
- Based on a range of commonly collected clinical parameters, who should receive a CRT-D device?

2.1.2 Patient population of interest

Adults with heart failure (NYHA I to IV) and LVEF ≤ 35%, and/or at risk of sudden cardiac death.

2.1.3 Interventions included

The approach used in the submission is predicated on the definition of a large number of patient subgroups using clinically relevant variables. The appraisal protocol listed four interventions of interest (optimal pharmacological therapy - OPT, ICD, CRT-P, and CRT-D), but not all have been included as comparators in all the patient subgroups in this submission. The rationale behind the choice of interventions for each subgroup is presented in Table 6. In general, the justification for exclusion is based on either contraindication (e.g. CRT not being recommended for patients with a QRS duration <120ms), or on a paucity of data, which has been used as a proxy for non-use in routine clinical practice.

Table 6: Rationale for excluding interventions from some subgroups

Treatment option	Subgroup from which excluded	Rationale/ justification
OPT	None	
ICD	NYHA IV	Minimal IPD data available from clinical trials *(of 12,638 patients included in IPD database only [redacted] were NYHA IV and randomised to an ICD)*
CRT-P	NYHA I/II	Minimal IPD data available from clinical trials *(of 12,638 patients included in IPD database only [redacted] were NYHA I-II and randomised to a CRT-P)*
	QRS <120ms	Prolonged QRS duration required for consideration of device insertion. No evidence of benefit from CRT in patients with normal QRS duration
CRT-D	QRS <120ms	Prolonged QRS duration required for consideration of device insertion. No evidence of benefit from CRT in patients with normal QRS duration

2.1.4 Role of left bundle branch block (LBBB) in decision problem definition

LBBB in the presence of HF has adverse haemodynamic effects and may be a treatment effect modifier for CRT therapy. There is evidence that HF patients with LBBB (particularly those with mildly symptomatic disease) may derive an increased survival benefit from CRT, which acts to reduce dyssynchrony (full discussion and references in section 1.1.5). For this reason, and in line with recently issued ESC guidelines,[4] we have viewed LBBB as a potentially important decision variable (that is, one that could be used in final guidance to define who gets which treatment, if any). Thus, all cost-effectiveness analyses have been stratified into patient subpopulations with and without LBBB.

LBBB status was not used to restrict the systematic review of clinical efficacy.

2.1.5 The role of atrial fibrillation (AF) in decision problem definition

Although AF is not considered a contraindication to CRT in clinical practice, patients with persistent AF were excluded from most of the RCTs identified. The resulting paucity of data on patients with AF in the clinical trial database (on

which all patient level analyses were performed) meant it was not possible to include AF amongst the list of potential baseline risk or treatment effect modifiers. Hence, the analyses presented in this submission will not distinguish between patients with and without AF.

AF status was not used to restrict the review of clinical efficacy.

2.1.6 Role of electrophysiology (EP) testing

Electrophysiology (EP) testing has been proposed as a tool for identifying patients at increased risk of sudden cardiac death. It has been argued that patients who do not have inducible ventricular tachycardia or fibrillation on EP testing are at lower risk of SCD. However, evidence from the MADIT-II and SCD-HeFT trials, and the MUSTT trial and registry, suggests that this is not a clinically useful method of risk stratification as 'inducible' and 'non-inducible' patients have a similar risk of sudden cardiac death. These findings have been incorporated into the most recent European guidelines[4], which do not include EP testing in their recommendations on device use.

EP testing is an invasive procedure involving the insertion of wires into the heart via leg veins. Rapid pacing is used to determine whether ventricular arrhythmias can be induced. This inevitably results in some inconvenience to the patient and is associated with a risk of complications. It carries the costs of the equipment, staff and procedure time and is available only at a limited number of centres in the UK. We are advised by clinical experts that EP tests, as specified in the guidance arising from TA95, no longer reflect best evidence-based practice. Therefore our analysis does not distinguish between patients on the basis of response to EP testing.

2.1.7 Other subgroups of interest

For the patient level data analyses we also considered NYHA class, ischaemic aetiology, LVEF, QRS duration, age and gender as potential subgroups of interest. However, in recognition that NICE would be unlikely to issue guidance contingent on age and gender in addition to LBBB status, we have defined subgroups on the basis of NYHA class (I/II/III/IV), QRS duration (less than 120ms, between 120ms and 149ms, at least 150ms) and ischaemic aetiology status.

2.1.8 Patient groups of interest in assessing ICD therapy

Individuals who meet the criteria laid out in TA95 for secondary prevention (in particular having survived a cardiac arrest) have a strong clinical indication for an ICD. Given the real term reduction in implant costs, as well as the absence of new studies in this patient group we believe that this patient group lies outside the scope of the current appraisal. Hence, we have focused solely on the use of ICD in a primary prevention setting.

Similarly, we have not included patients with a familial cardiac condition which results in a high risk of death in the analyses. These include, but are not restricted to, long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC). The rationale for this exclusion is that the available trials do not include data on these indications and thus information from smaller trials and registries represents the best available information on which to base these treatment decisions.

2.2 End points of interest in assessing clinical efficacy

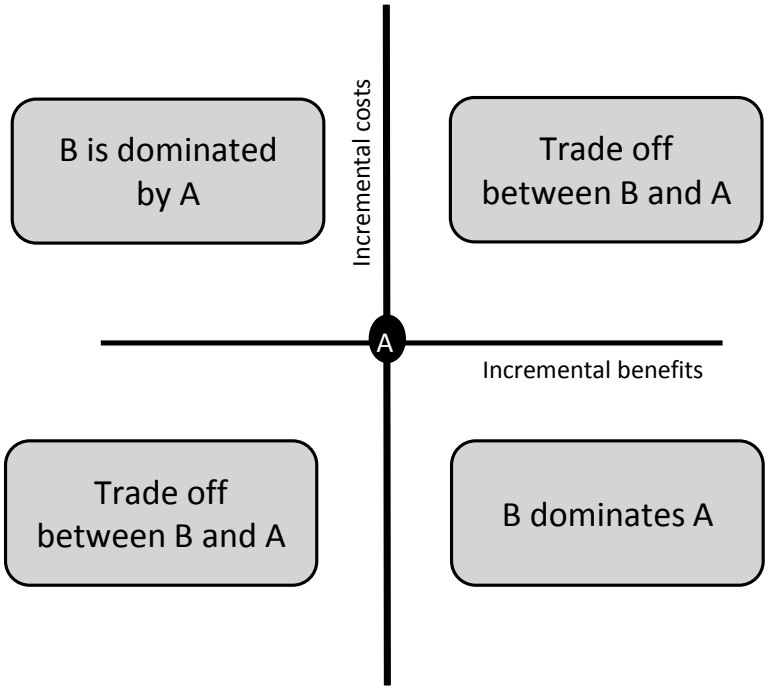
In line with the appraisal scope and with previous reports prepared by technology appraisal groups, we have focused on the following outcomes of interest:

- All-cause mortality
- Sudden cardiac death
- Death due to heart failure
- All cause hospitalisation
- Incidence of ventricular tachycardia/fibrillation
- Change from baseline in NYHA class
- Change from baseline in LVEF
- Treatment related serious adverse events
- Health Related Quality of Life (HRQoL) using Minnesota Living with Heart Failure Questionnaire (MLWHFQ)
- HRQoL using the EQ-5D questionnaire

2.3 Presentation of cost-effectiveness results

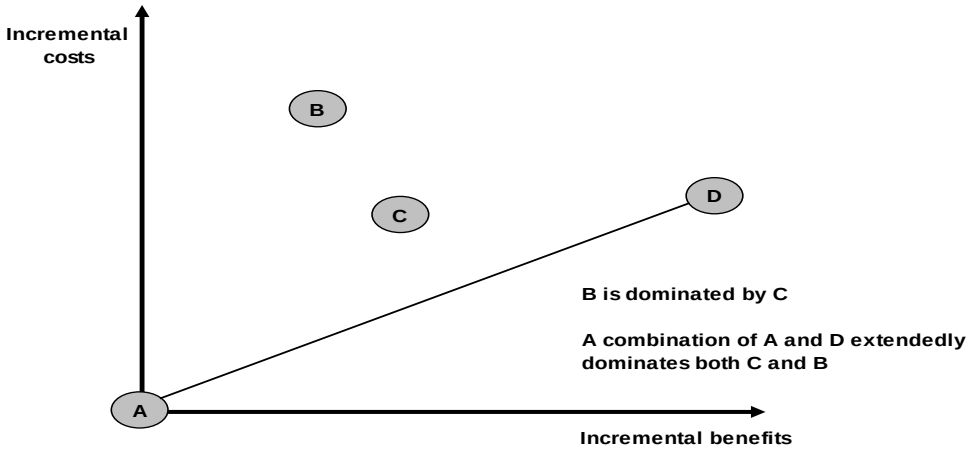
Deterministic results are presented in fully incremental format for all subgroups of interest. In order to interpret correctly the results presented in section six, it is important to be aware of a number of key concepts. In general, for a pairwise comparison of two interventions (B vs. A for simplicity), if the mean incremental results are in the bottom right quadrant of the cost effectiveness plane, corresponding to B being both cheaper and more beneficial than A, then intervention B "dominates" intervention A. Conversely, if the incremental results are in the top left quadrant of the cost-effectiveness plane, B is more expensive and less efficacious than A and is hence "dominated". In either of the two other quadrants of the cost-effectiveness plane, the ratio of incremental costs to incremental benefits is compared to different threshold values. The process is shown graphically in Figure 10.

Figure 10: Example cost-effectiveness plane



However, in situations where there are more than two interventions being compared, the concept of dominance needs to be modified, with the costs and benefits of each intervention being compared both to the option at the origin (the least costly and least effective) and also all other interventions. Combinations of treatments are also used to make comparisons ("extended dominance"). The general principle is shown in Figure 11.

Figure 11: Illustration of dominance and extended dominance



Clinical trial evidence and expert advice indicate that patients who have NYHA class III symptoms are at high risk of sudden cardiac death and may require ICD therapy (see Figure 1). Thus, because of the most recent ESC guidelines[4] and the large overlap in eligible patient populations in the current NICE CRT and ICD recommendations, patients who are in NYHA class III and meet the current NICE criteria for CRT are likely to have indications for CRT-D. The latest heart failure clinical guideline issued by NICE[5] also notes that ICD usage is higher up the 'decision tree'.

Thus, in this patient group, there is need for a comparison of defibrillation based alternatives (CRT-D or ICD) to OPT and also to each other (CRT-D to ICD). We have therefore provided head to head ICERs for these comparisons in all relevant patient groups, as well as a three-intervention incremental analysis, to allow the appraisal committee to incorporate existing clinical practice into their decision making.

Cost-effectiveness planes for all subgroups are presented in appendices. Because multiple comparisons are available for many of the subgroups of interest, conventional one-way parameter uncertainty analyses were not performed. Instead, fully incremental analyses were undertaken for a range of alternative structural approaches and parameter values.

Due to the computation intensive approach used to fully assess the impact of patient level heterogeneity on cost-effectiveness, a full probabilistic sensitivity analysis was not performed.

3 Clinical effectiveness: systematic review of the literature

- A systematic review of RCT evidence for clinical effectiveness of all interventions in the scope was carried out in accordance with NICE guidelines. Full details of methodology can be found in Appendices 1-5.
- The results of a formal evidence synthesis are presented in a separate section of the dossier.
- Qualitative narrative summaries are provided of mortality, other clinical, hospitalisation and health-related quality of life end points, and of adverse events.
- 46 articles reporting the results of 22 trials met the criteria for inclusion in the qualitative summary.
- The review confirms that there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF. This is backed up by several previously published meta-analyses.
- Additional evidence from long-term follow-up of two studies shows a persistent mortality benefit from both ICD and CRT.
- No new evidence was identified relating to the use of ICD in a secondary prevention setting.

The clinical effectiveness of all interventions included in the project scope was assessed by a systematic review of published randomised controlled trial (RCT) based research. This systematic review was executed in line with the requirements of NICE as stated in their methods guideline.[38] The aim was to summarise the literature on the clinical efficacy of ICD, CRT-P and CRT-D in all published randomised controlled trials. The results from a formal evidence synthesis of studies identified are presented in a separate section of the dossier. Narrative summaries of the studies identified are provided in this section. We also discuss the findings of previous meta-analyses.

Four of the studies are collecting long-term follow-up data on mortality, some of which became available after both the data lock date for the Individual Patient Data meta-analysis and date of search strategy execution. These data are discussed separately in Section 3.9.

3.1 Identification and assessment of studies

3.1.1 Search strategy

The systematic review was undertaken using the timelines initially provided by NICE to all technology sponsors. Hence, to identify potential relevant articles, electronic searches were conducted on the 27th and 28th of June 2011 in the following databases:

- Medline and Medline in process 1950 to present (OVID SP)
- EMBASE 1980 – present (OVID SP)
- Cochrane Central Register of Controlled Trials (CENTRAL)

All searches were limited to English language and start publication date of 1990. Further details of the search strategies are contained in Appendix 1. To further ensure all relevant articles have been identified, we scanned the reference list of full text papers retrieved from the searches.

3.1.2 Inclusion and exclusion criteria

Studies were selected according to the following criteria:

Population

- Adults with LVEF ≤40% or those who may not have (LVEF) ≤40% but are considered to be secondary prevention patients according to TA95 criteria (see Section 1.5.2)
- Adults who have experienced prior myocardial infarction (MI) or coronary revascularisation; this must have occurred more than 45 days prior to enrolment.

Interventions

Studies comparing any two or more of the following treatments (including at least one device) were included:

- Implantable cardioverter defibrillator (ICD)
- Cardiac resynchronisation therapy with a pacing device (CRT-P)
- Cardiac resynchronisation therapy with a defibrillator device (CRT-D)
- Placebo
- Medical therapy
  - Optimal pharmacological therapy (OPT): For inclusion in the trial patients must be on a particular drug regimen with stable doses before randomisation. A common synonym used in the literature is optimal medical therapy (OPT). these two have both been used in this dossier and refer to the same treatment option.
  - Conventional medical therapy (CMT): Patients included in the trial are not required to be on a particular drug regimen before randomisation.

Study type

Full publications of randomised controlled trials (RCTs) from the start of 1990.

Exclusion criteria

The following criteria were used to exclude studies from the review:

- Patients with familial cardiac conditions with a high risk of SCD, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and following surgical repair of Tetralogy of Fallot
- Non English-language publications
- Conference abstracts and non-randomised controlled trials.
- Trials comparing different variant of the same device (e.g. comparisons of different pacing strategies).

3.1.3 Study selection

The selection of studies was undertaken by two reviewers. After de-duplication, articles were screened at title and abstract level. Those that met the eligibility criteria stated above were selected for full article review. Articles that did not meet the inclusion criteria from the full text review were excluded with reasons and

documented in the PRISMA flow diagram in Appendix 2.

3.1.4 Data extraction

Data were extracted for the following variables:

Study characteristics

Author, year, study duration, sample size

Baseline characteristics

- Age
- Gender
- QRS Duration
- NYHA class
- LVEF
- History of MI
- History of AF
- Aetiology status
- Incidence of LBBB
- History of prior pacing
- Normal sinus rhythm
- Randomisation

End points of interest

- All-cause mortality
- Sudden cardiac death
- Death due to heart failure
- All cause hospitalisation
- Incidence of ventricular tachycardia/fibrillation
- Change from baseline in NYHA class
- Change from baseline in LVEF
- Device related serious adverse events
- Quality of life using Minnesota Living With Health Failure questionnaire (MLWHFQ) and the EQ-5D (these were the most commonly used quality of life instruments in cardiovascular diseases).

A standardised data extraction form was designed and tailored to the review (n.b. this form can be made available to the academic review group on request). Data were not extracted for secondary prevention of SCD studies (survivors of sudden cardiac events or patients with recurrent unstable rhythms). The rationale for this is presented in section 2.1.8.

3.1.5 Assessment of risk of bias

Two independent reviewers critically appraised the quality of included studies according to the criteria specified by NICE which is based on the evaluation of all components of the trial that could affect the risk of bias[38] (see Appendix 3 for further details).

3.2 Studies identified by the review

A total of 7860 articles were retrieved: 7858 from the electronic databases, the summary of safety and effectiveness data from one trial (Rhythm ICD[39]) were provided by the manufacturer and the summary of another study (VeCtoR[40]) was identified from the reference list of retrieved papers. Of these, 46[8;39-83] articles reporting results of 22 trials were included in the qualitative synthesis of the review of relative treatment effects. An additional 11[84-94] articles reporting results of five trials on secondary prevention patients were identified. Data were not extracted for these six trials as explained above, and references are provided in appendix four for completeness. Further details on the study selection process can be found in the PRISMA flow diagram in Appendix 2.

The studies included in the qualitative synthesis are summarised in Table 7.

Note about the REVERSE trial

The REVERSE trial[63-65] was an international multicentre, randomised, double-blind controlled trial conducted in United States, Canada and Europe. The trial enrolled patients with NYHA class I and II heart failure.

Patients underwent implantation of a CRT system with or without ICD capabilities. To receive an ICD the patient had to have a class I or II indication for an ICD according to US and Canadian guidelines. In Europe, the ICD implantation was left to physicians' judgement based on European guidelines. A CRT-ICD (CRT-D) was implanted in 83.4% and a CRT pacemaker (CRT-P) in 16.6% of patients and they were randomised to CRT-ON and CRT-OFF.

Therefore the trial included the following interventions:

- Patients with a CRT-D implanted (83.4%):
  - CRT-ON- delivered therapy: CRT-D

  - CRT-OFF- delivered therapy: ICD
- Patients without an ICD (i.e. CRT-P implanted) (16.6%):
  - CRT-ON: delivered therapy: CRT-P
  - CRT-OFF: inactive pacing

Results were provided for the total group of patients randomised to CRT-OFF and CRT-ON. Data were not stratified for those patients that received an ICD and those without and ICD. As most of the patients in the trial received an ICD, in order to simplify the presentation in the tables, the interventions have been described as patients receiving CRT-D and randomised to CRT-ON and CRT-OFF. This information should be taken into account when reading the data extraction tables.

Note about medical therapy

As stated in the inclusion criteria, there were two types of medical therapy interventions according to whether patients were required to be on a particular drug regimen before randomisation (OPT) or there were no requirements for a particular drug regimen before randomisation (CMT).

A statement indicating that patients were required to be on OPT was present in the following studies: CARE-HF, COMPANION, CONTAK-CD, MADIT CRT, MIRACLE, MIRACLE-ICD, MIRACLE ICD II, MUSTIC, RAFT, RESPOND, RETHINQ, REVERSE, RHYTHM-ICD, Piccirillo *et al*., Pinter *et al*., SCD-HeFT and Vector.

No statement regarding requirements for a particular medical therapy before randomisation was present in the following studies: AMIOVIRT, DEFINITE, CAT, MADIT and MADIT II. These studies therefore have been categorised as patients receiving CMT.

In order to simplify the presentation in the tables, the interventions for medical therapy have been collectively described as OPT. This should be taken into account when reading the tables.

3.3 Baseline patient characteristics

A summary of treatments used in each study, as well as patient counts and the list of all relevant references is presented in Table 7. Details of patients that

crossed over from intervention to control arms are described in Table 8.The characteristics of patients at the baseline are summarised by LVEF and NYHA distribution in Table 9, by demography and QRS morphology in Table 10 and by cardiovascular history in Table 11.

Table 7: Summary of treatments and randomisation in each trial

Study	Randomised	Implanted	Randomisation	Delivered therapy	Max Follow up (months)	Number enrolled	Number randomised	Protocol mandated cross-over
AMIOVIRT[79;82]	Before implantation	ICD	ICD	ICD	24 (15.6)[1.2-57.6][a]	NR	103	No
		None	OPT	OPT				
CARE-HF[8;55-58]	Before implantation	CRT-P	CRT-P	CRT-P	37.6 (31.5-42.5)[b]	NR	813	No
		None	OPT	OPT				
CAT[341;42;47]	Before implantation	ICD	ICD	ICD	66 (26.4)[d]	104	104	No
		None	OPT	OPT				
COMPANION[46;51-53]	Before implantation	CRT-P	CRT-P	CRT-P	16.5[e]	NR	1520	No
		CRT-D	CRT-D	CRT-D	16[e]			
		None	OPT	OPT	14.8[e]			
Contak-CD[60;76]	Before implantation	CRT-D	CRT-ON	CRT-D	6[f]	581	490	Yes
		CRT-D	CRT-OFF	Inactive pacing				
DEFINITE[62;73]	Before implantation	ICD	ICD[ɤ]	ICD	29.0 (14.4)[g]	NR	458	No
		None	OPT	OPT				
MADIT [68;69]	Before implantation	ICD	ICD	ICD	27[h]	196[i]	196	No
		None	OPT	OPT				
MADIT CRT[67;77;95]	Before implantation	CRT-D	CRT-D	CRT-D	28.8[h]	NR	1820	No
		ICD	ICD	ICD				
MADIT II[70;71]	Before implantation	ICD	ICD	ICD	91.2 (42 to 108)[j]	1232	1232	No
		None	OPT	OPT				
MIRACLE[43;45;61]	After implantation	CRT-P	ON	CRT-P	6	571	453[k]	No

Study	Randomised	Implanted	Randomisation	Delivered therapy	Max Follow up (months)	Number enrolled	Number randomised	Protocol mandated cross-over
		CRT-P	OFF	Inactive pacing				
MIRACLE-ICD[83]	After implantation	CRT-D	CRT-ON	CRT-D	6	639	369	No
		CRT-D	CRT-OFF	Inactive pacing				
MIRACLE-ICD II[44]	After implantation	CRT-D	CRT-ON	CRT-D	6	222	186	No
		CRT-D	CRT-OFF	Inactive pacing				
MUSTIC[54]	After implantation	CRT-P	ON	CRT-P	6	67	58	Yes
		CRT-P	OFF	Inactive pacing				
Piccirillo *et al*[74]	Before implantation	ICD	ICD	ICD	12	NR	31	No
		CRT-D	CRT-D	CRT-D				
Pinter *et al*[75]	After implantation	CRT-D	CRT-ON	CRT-D	6	90	72	No
		CRT-D	CRT-OFF	Inactive pacing				
RAFT[80;81]	Before implantation	CRT-D	CRT-D	CRT-D	40 (20)[g]	179[h]	179[h]	No
		ICD	ICD	ICD				
RESPOND[59]	Before implantation	CRT-P	CRT-P	CRT-P	22.3[l]	110	60	No
		None	OPT	OPT				
RETHINQ[49;50]	After implantation	CRT-D	CRT-ON	CRT-D	6	250	172	No
		CRT-D	CRT-OFF	Inactive pacing				
REVERSE[63-65;78]	After implantation	CRT-D	CRT-ON	CRT-D	12	684	610	No
		CRT-D	CRT-OFF	ICD				
Rhythm-ICD[39]	After implantation	CRT-D	CRT- ON	CRT-D	12.1 (3.4)[g]	205	178	No
		CRT-D	CRT- OFF	Inactive pacing				
SCD-HeFT[48;72]	Before implantation	ICD	ICD	ICD	45.5[e]	NR	2521	No

Study	Randomised	Implanted	Randomisation	Delivered therapy	Max Follow up (months)	Number enrolled	Number randomised	Protocol mandated cross-over
		None	Amiodarone	OPT				
		None	OPT	OPT				
Vector[40]	Before implantation	CRT-P	ON	CRT-P	19.9 (8.9)[g]	144	106	No
		CRT-P	OFF	OPT				

a - Mean (SD) [range] reported in years, and converted into months; **b** - Data obtained from Cleland 2006. It represents median (IQR) for longer follow up for mortality. Mean FU for hospitalisation is 29.4 months as reported in main publication 2005; **c**- Presented result of a pilot study; **d**- maximum follow up in mean (SD) reported in years, then converted into months; **e**- Follow up reported as median months of follow up; **f**- Study treatment phase 6 months, length of long-term follow-up phase unknown; **g**- reported as mean follow up (standard deviation); **h**- Mean follow-up; **i**- the author reported that there may have been selection bias during enrolment because a consistent log of eligible who did not qualify on the basis of electrophysiology study was not kept; **j**- Median Follow up (interquartile range) reported in years and converted into months; **k-** 47 patients were not enrolled (device not successfully implanted n=43, patient required cardiac pacing n=2, patient's condition became clinically unstable n=2. 71 patients agreed to be enrolled in an initial pilot phase of the study which followed patients for only three months; **l**- Median FU, reported in days, converted into months; **NR** - not reported

Table 8: Summary of patient crossover in all included studies

Study	Details of crossovers	Details of data analyses as reported from the paper
AMIOVIRT	Amiodarone (n=52); ICD (n=51) 25 patients initially treated with amiodarone had the drug discontinued because of adverse side effects 17.8 +/- 13.3 months (range 1.2 to 43.8 months) after initiation of therapy. 8 patients initially treated with amiodarone were later implanted with an ICD while 11 patients in the ICD group received amiodarone	Cut off for analysis: Study enrolment was discontinued at the first scheduled interim analysis of the first 10 deaths (September 2000). Stopping rule: mortality difference at a significance level of < 0.025 or a significance level of > 0.025 (90% power). The mean duration of follow-up was 2.0 +/- 1.3 years (range 0.1 to 4.8). All analyses were based on the intention-to-treat principle. Information from Wijetunga and Strickberger 2003- AMIOVIRT was conducted from August 1996 to June 2001
CARE-HF	Data from the extension study (8 months extension): 19 out of 409 patients assigned to CRT-P did not receive the device and 95 of 404 in OPT group received a CRT device and had it activated during follow-up. (Cleland et al.[57]).	Prior to study closure, an extension phase lasting a further 8 months (allowing time for data analysis and presentation) was declared during which cross-over was discouraged. Data lock occurred in January 2005. Results were presented in March 2005. Although knowledge of the results would be expected to lead to an increase in cross-over from assigned therapy, the Steering Committee considered that this would have little effect on the results before May 2005, as investigators would probably not been able to act immediately on the findings. Median follow-up time was 37.6 months (range 26.1-52.6). All analyses were based on intention-to-treat principle.
CAT	Number of patients cross-over was not reported.	
COMPANION	26% of patients in OPT arm withdrew from the optimal medical therapy to receive commercially available implants due to arrhythmia or Heart Failure. Withdrawal rate for the CRT-P arm was 6% and for the CRT-D 7%.	To mitigate the withdrawal rate patients who withdrew were asked to consent to the collection of data on vital status and hospitalisations for the duration of the trial. Data on patients who withdrew before reaching an end point who were not known to have died and for whom complete post-withdrawal information on hospitalisation could not be obtained were censored at the time of elective hospitalisation for device implantation or on the day of last contact. For the mortality end point analysis, data on patients whose vital status was not known at the end of the study were censored on the date of the last known contact. All analyses were censored at the time

		of cardiac transplantation. Each of the devices used in the study became commercially available during the trial. Since this was an open-label study, the subsequent event was a disproportionately high rate of withdrawal from the OPT so that patients could receive cardiac-resynchronisation therapy with one of these devices. This change was particularly common in patients with ischaemic cardiomyopathy, for whom such treatment became an option with the publication of MADIT II. Authors addressed this disproportionate rate by excluding elective implantation of devices from analyses of the primary end point and other hospitalisation end points and obtaining consent of patients who withdrew to complete the ITT analyses. All analyses were conducted according to the intention-to-treat
CONTAK-CD	This was a cross-over study. Patients with an ICD were randomised to pacing (CRT-D) or no pacing (IDC) and crossed over at 3 months (Phase I) until end of study (6 months) at the end of these therapy phases, pacemaker programming was left to the discretion of the investigator. The study design was modified (Phase II) from cross-over to parallel design.	Patients in phase I contributed data from a three month treatment phase and patients in phase II contributed data from a six-month treatment phase.
DEFINITE	Patients who were randomised to OPT were allowed to receive an ICD if they had a cardiac arrest or an episode of unexplained syncope. 27 crossovers occurred: Of the 229 in the OPT arm 23 (10%) received an ICD and of the 229 patients in the ICD group 4 either did not undergo implantation of the ICD, had the device explanted or inactivated. All 4 patients were included in the ITT analysis.	This report presents the results of the final analysis at the time of the 68th death. The first patient underwent randomisation on July 9 1998, and the 458th patient underwent randomisation on June 6, 2002. The 68th death occurred on May 25, 2003.
MADIT	OPT (n=101), ICD (n=96). 16 patients crossed over, 11 in OPT and 5 in the ICD group	Data were analysed weekly beginning at the point at which 10 deaths had been reported. Because of the slow rate of enrolment and before the first patient enrolled had reached the 5th year of the study, in was decided in Nov 12, 1995 that data on patients will be censored for analytical purposes at five years. The efficacy boundary of the sequential designed was crossed when 51 deaths were reported, and the study was officially stopped at that time. All analyses were conducted according to the intention-to-treat principle.
MADIT CRT	A total of 173 crossovers occurred. 91 (12.4%) patients who were assigned to ICD only group received a CRT-D device, while 82 (7.5%) patients assigned to CRT-D group subsequently received an ICD only therapy. Devices were removed in 14 patients (1.3%) in the CRT-D arm and 5 patients (0.7%) in the	The trial was stopped on June 22, 2009, shortly after the 9th of 20 planned analyses since the monitoring statistics had reached the prespecified efficacy boundary. Study-group assignments were then unblinded, an all analyses were limited

	ICD arm. 44 patients in the CRT-D arm (4%) and 55 in the ICD arm (7.5%) declined to continue participating in the study, were withdrawn or lost-to-follow up.	to events occurring before trial termination.
MADIT II	There were 202 crossovers: Among the 742 patients in the ICD arm 22 did not receive an ICD after randomisation and 13 had the ICD extracted during the trial; among the 490 patients in the OPT group. 27 crossed over to the ICD arm during the trial, and 140 received an ICD within 4 months after trial closure.	The trial began on July 11, 1997 and stopped on November 20, 2001 shortly after analyses revealed the prespecified efficacy boundary was reached. The primary analysis was carried out including data on crossover between the treatment arms and the consistency of the results was further validated in an intention-to-treat analysis.
MIRACLE	Crossover from the control group to CRT-P group before the six months study period was prohibited, except for patients in whom a bradyarrhythmia requiring cardiac pacing developed. As a result, 10 patients in the control group had their device reprogrammed to the cardiac- resynchronisation mode.	Patients were recruited between November 1998 and December 2000. Study duration, six months. Patients randomised to the ON or OFF group who had their pulse generator turned OFF or ON before the 6months duration of the study had their safety data included in the statistical analysis; however their efficacy data was not pooled with that of the rest population. Analyses were performed according to the ITT principle.
MIRACLE-ICD	14 (8%) patients in the control group and 10 (5%) patients in the CRT-D crossed over before the end of randomisation phase	Study conducted from October 1, 1999 to August 31, 2001. Duration of the study, 6 months. The low incidence of crossovers had no effect on the results of analyses, which were performed on an ITT basis.
MIRACLE-ICD II	7 crossovers occurred before the end of the trial: 5 (5%) patients in the inactive-pacing group and 2 (2%)in the CRT-D group	Analyses were performed according to the ITT principle.
MUSTIC	This was a cross-over study. Patients were randomised to three months each of inactive pacing and active pacing. During inactive pacing, one patient had severe decompensation leading to premature switch to active pacing.	Analyses were performed according to the ITT principle. Efficacy end points were assessed only in patients with no missing data after the completion of both crossover phases.
PICCIRILLO *et al*	Number of patients cross-over was not reported.	
PINTER *et al*	CRT-D (n=36), ICD (n=36). Two patients crossed over. 1 patient in the CRT-D group and another in the ICD group.	Cross over patients were regarded as patients who did not complete the study. It appears data from these patients were not included in the analyses.
RAFT	53 patients (6.0%) in the CRT-D group did not receive CRT device. 36 patients (4.0%) in the ICD arm crossed over before the occurrence of the primary outcome and 60 (6.6%) after hospitalisation for heart failure. Mean follow up 40 months.	Patients were recruited from January 2003 through February 2009. Analyses were performed according to the ITT principle.
RESPOND	CRT-P (n=29), OPT (n=31). 1 patient crossed over from OPT to CRT after development of sustained ventricular tachycardia. Median follow-up 677,5 days.	Analyses were performed according to the ITT principle. No censoring was carried out at 6 months.

RETHINQ	ICD (n=85), CRT-D (n=87). 3 patients in the ICD arm crossed over to CRT-D. No patients in the CRT-D crossed over to ICD.	Analyses were performed according to the ITT principle. Data for all patients were censored at 196 days, the last day of the 6-month window for clinical visits.
REVERSE	ICD (n=191), CRT-D (n=419). Cross-over from the assigned treatment mode was prohibited before the 12-months assessment, except patients who experienced chronic worsening of heart failure. There were 20 permanent cross overs in 12 months: 6 patients in the CRT-D and 14 in the ICD group crossed over.	Analyses were performed according to the ITT principle.
RHYTHM-ICD	CRT-D (n=119), ICD (n=59). Cross-over from the control group was allowed after completing 6-months follow up visit. Two patients crossed over from the CRT OFF group to the CRT ON group before their 6-month follow-up visit. Mean follow-up 12.1 patient months.	Analyses were performed according to the ITT principle.
SCD-HeFT	Amiodarone (n=845), Placebo (n=847), ICD therapy (n=829). Of the 829 patients in the ICD group, 17 (2%) declined to undergo implantation and implantation was unsuccessful in one. An additional 32 patients (4%) had their ICD removed during follow-up.188 patients (11%) in the drug groups crossed over to receive ICD therapy during follow up. Median time from randomisation to cross-over is 26.7months. Median follow-up was 45.5 months.	Analyses were performed according to the ITT principle.
VECTOR	Cross-over into the CRT-P treatment group was at physician's discretion. However number of patients that crossed over was not reported.	

Table 9: Baseline patient characteristics by NYHA class and LVEF

Study	Arm	NYHA I n (%)	NYHA II n (%)	NYHA III n (%)	NYHA IV n (%)	LVEF- Mean (SD)
AMIOVIRT	ICD	10 (18)	33 (64)	8 (16)	0	0.22 (0.10)
	OPT	7(13)	33 (63)	12 (24)	0	0.23 (0.08)
CARE-HF	CRT-P	0	0	386 (94)	23 (6)	25 (21-29)[1]
	OPT	0	0	377 (93)	27 (7)	25 (22-29)[1]
CAT	ICD	0	33 (66.7)	17 (33.3)	0	24 (6)
	OPT	0	35 (64.1)	19 (35.8)	0	25 (8)
COMPANION	CRT-P	0	0	536 (87)	81 (13)	0.202
	CRT-D	0	0	511 (86)	84 (14)	0.222
	OPT	0	0	252 (82)	56 (18)	0.222
Contak-CD	CRT-D	0	78 (32)	147 (60)	20(8)	21 (7)
	ICD	0	81 (33)	140 (57)	25 (10)	22 (7)
DEFINITE	ICD	58 (25.3)	124 (54.2)	47 (20.5)	0	20.9 (7 - 35)[3]
	OPT	41 (17.9)	139 (60.7)	49 (21.4)	0	21.8 (10 - 35)[3]
MADIT	ICD	NR	636		0	0.27 (0.07)
	OPT	NR	677		0	0.25 (0.07)

Study	Arm	NYHA I n (%)	NYHA II n (%)	NYHA III n (%)	NYHA IV n (%)	LVEF- Mean (SD)
MADIT II	ICD	260 (35)	260 (35)	186 (25)	37(5)	23 (5)
	OPT	191 (39)	167(34)	113(23)	20 (4)	23 (6)
MADIT-CRT	CRT-D	152 (14.0)	937 (86)	0	0	0.24 (0.05)
	ICD	113 (15.5)	618 (84.5)	0	0	0.24 (0.05)
MIRACLE	CRT-P	0	0	205 (90)	23 (10)	21.8 (6.3)
	OPT	0	0	205 (91)	20 (9)	21.6 (6.2)
MIRACLE-ICD	CRT-D	0	0	165 (88.2)	22 (11.8)	24.2 (6.5)
	ICD	0	0	163 (89.6)	19 (10.4)	23.9 (6.0)
MIRACLE-ICD II	CRT-D	0	85 (100)	0	0	24.4 (6.6)
	ICD	0	101 (100)	0	0	24.6 (6.7)
MUSTIC	First study group (1-CRT-P active-2 CRT-P inactive)	0	0	29 (100)	0	
	Second study group (1-CRT-P inactive- 2 CRT-P active)	0	0	29 (100)	0	23 (7)[4]
Piccirillo *et al*	ICD	0	0	5 (33)	10(67)	22 (8)
	CRT-D	0	0	5 (31)	11 (69)	23 (4)
Pinter *et al*	CRT-D	NR	NR	NR	NR	21.2 (7.9)
	ICD	NR	NR	NR	NR	24 (8.3)

Study	Arm	NYHA I n (%)	NYHA II n (%)	NYHA III n (%)	NYHA IV n (%)	LVEF- Mean (SD)
RAFT	CRT-D	0	708 (79.2)	186 (20.8)	0	22.6 (5.4)
	ICD	0	730 (80.8)	174 (19.2)	0	22.6 (5.1)
RESPOND	CRT-P	0	0	19(65.5)	10(34.5)	22.3 (8.42)
	OPT	0	0	26(83.9)	5(16.1)	22.1 (10.2)
RETHINQ	CRT-D	0	0	87 (100)	0	25 (5)
	ICD	0	0	84 (99)	0	26 (6)
REVERSE	CRT-D	75 (18)	344 (82)	0	0	26.8 (7.0)
	ICD	32 (17)	159 (83)	0	0	26.4 (7.1)
Rhythm-ICD	CRT-D	1 (0.8)	6 (5.0)	104 (87.4)	8 (6.7)	25.6 (8.3)
	ICD	2 (3.4)	4 (6.8)	50 (84.7)	3 (5.1)	23.3 (6.4)
SCD-HeFT	ICD	0	566 (68)	263 (32)	0	24 (19.0-30.0)[1]
	Amiodarone	0	594 (70)	253 (30)	0	25 (20.0-30.0)[1]
	Placebo	0	594 (70)	253 (30)	0	25 (20.0-30.0)[1]
Vector	CRT-P	0	NR[4]	NR[4]	NR[5]	NR
	OPT	0	NR[4]	NR[4]	NR[5]	NR

1.Median LVEF (IQR); **2**- Median LVEF; **3-**Mean LVEF (range); **4-** Mean LVEF (SD) for all the patients at baseline; **5-**NYHA was not reported by intervention group. 29%, of patients were NYHA class II, 65% were NYHA class III and 6% were NYHA class IV of 106 patients randomised and 38 who were not randomised; **6**- 63% 0f patients in the ICD groups had NYHA class II or III; **7**- 67% of patients in the OMT group had NYHA class II or III. **NR:** not reported

Table 10: Baseline patient characteristics: demography and QRS Morphology

Study reference	Arm	Age- mean (SD)	Male- n (%)	QRS duration (ms)- Mean (SD)	LBBB-n (%)
AMIOVIRT	ICM	58 (11)	34 (67)	NR	21(42)
	OPT	60 (12)	38 (74)	NR	27 (53)
CARE-HF	CRT-P	67 (60-73)[1]	304 (74)	160 (152-180)[1]	NR
	OPT	66 (59-72)[1]	293 (73)	160 (152-180)[1]	NR
CAT	ICD	52(12)	43 (86)	102(29)	42 (84.6)
	OPT	52(10)	40(74)	114(29)	44 (81.8)
COMPANION	CRT-P	67[2]	413 (67)	160[2]	425 (69)
	CRT-D	66[2]	398 (67)	160[2]	434 (73)
	OPT	68[2]	212 (69)	158[2]	215 (70)
Contak-CD	CRT-D	66 (11)	208 (85)	160(27)	132 (54)
	ICD	66(11)	203 (83)	156(26)	135 (55)
DEFINITE	ICD	58.4 (20.3-83.9)[3]	166 (72.5)	114.7 (78 - 196)[3]	45 (19.7)
	OPT	58.1 (21.8-78.7)[3]	160 (69.9	115.5 (79 -192)[3]	45 (19.7)
MADIT	ICD	62 (9)	92 (97)	NR	7 (7)
	OPT	64 (9)	92 (91)	NR	8 (8)

Study reference	Arm	Age- mean (SD)	Male- n (%)	QRS duration (ms)- Mean (SD)	LBBB-n (%)
MADIT II	ICD	64 (10)	623 (84)	50[4]	141 (19)
	OPT	65 (10)	417 (85)	51[4]	88 (18)
MADIT-CRT	CRT-D	65 (11)	814 (74.7)	699 (64.2)[5]	761 (69.9)[6]
	ICD	64 (11)	553 (75.6)	476 (65.1)[5]	520 (71.3)[6]
MIRACLE	CRT-P	63.9 (10.7)	155 (68)	167 (21)	NR
	OPT	64.7 (11.2)	153 (68)	165 (20)	NR
MIRACLE-ICD	CRT-D	66.6 (11.3)	142 (75.9)	165 (22)	NR
	ICD	67.6 (9.2)	141 (77.5)	162 (22)	NR
MIRACLE-ICD II	CRT-D	63.0 (12.8)	75 (88.2)	166 (25)	NR
	ICD	63.1 (12.1)	91 (90.1)	165 (23)	NR
MUSTIC	First study group	64 (11)	19 (65)	172(22)	877
	Second study group	64 (8)	24 (82)	175 (19)	
Piccirillo *et al*	ICD	65(8)	12(80)	159(8)	NR
	CRT-D	65(4)	13(81)	160(4)	NR
Pinter *et al*	CRT-D	66.3 (8.6)	28 (77.8)	NR[8]	NR
	ICD	66.1 (8.8)	29 (80.6)	NR[8]	NR
RAFT	CRT-D	66.1 (9.3)	758 (84.8)	157 (23.6)[9]	68 (7.6)

Study reference	Arm	Age- mean (SD)	Male- n (%)	QRS duration (ms)- Mean (SD)	LBBB-n (%)
	ICD	66.2 (9.4)	732 (81.0)	158.3(24)[9]	93 (10.3)
RESPOND	CRT-P	66.7(7.86)	25(86.2)	91.5(10.6)	NR
	OPT	69.3(10.2)	24(77.4)	97.8(12.9)	NR
RETHINQ	CRT-D	60 (12)	62 (12)	107 (12)	NR
	ICD	58 (14)	49 (58)	106 (13)	NR
REVERSE	CRT-D	62.9 (10.6)	327 (78)	153 (21)	NR[10]
	ICD	61.8 (11.6)	152 (80)	154 (24)	NR
Rhythm-ICD	CRT-D	NR[11]	NR	169 (16)	NR
	ICD	NR	NR	167 (15)	NR
SCD-HeFT	ICD	60.1 (51.9-69.2)[1]	639 (77)	NR	NR
	OPT	59.7 (51.2-67.8)1	655 (77)	NR	NR
Vector	CRT-P	NR[12]	NR[12]	NR	NR
	OPT	NR[12]	NR[12]	NR	NR

1-Median (IQR); **2**- Median; **3**- Mean (range); 4- Percentage of patients with QRS interval ≥0.12 sec; **5**- = number (percentage) of pts. With QRS duration ≥150 ms; **6**- LBBB was analysed amongst a total of 1088 and 729 pts. In the CRT-D & ICD respectively; **7**- Percentage of patients with LBBB for all the patients at baseline; **8**- Eligibility criteria was QRS >120 ms. However, data were not reported at baseline; **9**- Intrinsic QRS duration. And this was analysed amongst 826 and 837 patients in the CRT-D and ICD group respectively; **10**- 468 (76.7%) of all the patients in the trial had LBBB. Data not reported by intervention groups; **11**- Data not provided by intervention groups. Patients ≥18 years were eligible to enter the trial; **12**- Data not provided by intervention groups. The mean age (SD) and number (percentage) of male of the entire population = 67.1 (9.7) and 90 (62.5) respectively. NR = not reported

Table 11: Characteristics by cardiac history (n (%))

Study reference	Intervention	Prior MI	Ischaemic	History AF	Prior pacemaker	Non-sinus rhythm
AMIOVIRT	ICM	NR	0[1]	NR	NR	NR
	OPT	NR	0[1]	NR	NR	NR
CARE-HF	CRT-P	NR[2]	165 (40)	0	0	409 (100)
	OPT	NR[2]	144 (36)	0	0	404 (100)
CAT	ICD	0	NR	10 (20.4)	0	40 (79.6)
	OPT	0	NR	6 (11.3)	1 (1.9)	47 (86.8)
COMPANION	CRT-P	NR	333 (54)	0	0	617 (100)
	CRT-D	NR	327 (55)	0	0	595 (100)
	OPT	NR	182 (59)	0	0	308 (100)
Contak-CD	CRT-D	NR	164 (67)	NR	NR	NR
	ICD	NR	174 (71)	NR	NR	NR
DEFINITE	ICD	NR	0	52 (22.7)	0	NR
	OPT	NR	0	60 (26.2)	0	NR
MADIT	ICD	95 (100)	95 (100)	NR	2 (2)	NR
	OPT	101 (100)	101 (100)	NR	7 (7)	NR
MADIT II	ICD	742 (100)	742 (100)	67 (9)	NR	NR

Study reference	Intervention	Prior MI	Ischaemic	History AF	Prior pacemaker	Non-sinus rhythm
	OPT	490 (100)	490 (100)	39 (8)	NR	NR
MADIT-CRT	CRT-D	NR	598 (55)	118[3]	0	1089 (100)
	ICD	NR	401 (55)	90[3]	0	731 (100)
MIRACLE	CRT-P	NR	114 (50)	NR	0	NR
	OPT	NR	130 (58)	NR	0	NR
MIRACLE-ICD	CRT-D	NR	119 (64)	NR	NR	NR
	ICD	NR	138 (75.8)	NR	NR	NR
MIRACLE-ICD II	CRT-D	NR	47 (55.3)	NR	0	NR
	ICD	NR	59 (58.4)	NR	0	NR
MUSTIC	First study group	NR	NR	0	NR	29 (100)
	Second study group	NR	NR	0	NR	29 (100)
Piccirillo *et al*	ICD	NR	15 (100)	0	0	15 (100)
	CRT-D	NR	16 (100)	0	0	16 (100)
Pinter *et al*	CRT-D	24 (66.7)	NR	6 (16.7)	0	36 (100)
	ICD	27 (75)	NR	2 (5.6)	0	36 (100)
RAFT	CRT-D	NR	614 (68.7)	114 (12.8)	68	780 (87.2)
	ICD	NR	587 (64.9)	115 (12.7)	67	789 (87.3)

Study reference	Intervention	Prior MI	Ischaemic	History AF	Prior pacemaker	Non-sinus rhythm
RESPOND	CRT-P	0	22(75.9)	NR	NR	29 (100)
	OPT	0	28(90.3)	NR	NR	31 (100)
RETHINQ	CRT-D	NR	47 (54)	NR	0	NR
	ICD	NR	43 (51)	NR	0	NR
REVERSE	CRT-D	NR[4]	236 (56)	NR[5]	0	419 (100)
	ICD	NR[4]	97 (51)	NR[5]	0	191 (100)
Rhythm-ICD	CRT-D	NR	NR[6]	NR	NR	NR
	ICD	NR	NR[6]	NR	NR	NR
SCD-HeFT	ICD	NR	431	141 (17)	NR	NR
	OPT	NR	453	117 (14)	NR	NR
Vector	CRT-P	NR	NR	NR	NR	NR
	OPT	NR	NR	NR	NR	NR

1-Only pts. with non-ischaemic dilated cardiomyopathy and non-sustained ventricular tachycardia were included; **2**- 31% of patients from the entire study population had a history of MI. Data not provided by intervention groups; **3**- The number of patients who had AF was analysed for 1063 patients in the CRT-D and 717 in the ICD group; **4**- 281 (46.1%) of all the patients in the trial had a history of MI. Data not provided by intervention groups; **5**- 89 (14.6%) of all the patients in the trial had a history of AF. Data not provided by intervention groups; **6**- patients with Ischaemic and non-ischaemic HF were included. However the number (percentage) of patients who had ischaemic aetiology at baseline was not reported **NR** = not reported

3.4 Results from mortality end points

3.4.1 All-cause mortality

All-cause mortality was reported in the 22 trials (Table 12). A formal review of the impact of treatment on mortality is confounded by two key variables: differing follow up periods and interventions being used in patients with differing underlying disease profiles. A formal analysis of the impact of a range of clinical covariates forms a key element of the patient level network meta-analysis described in Section 4.

CRT-P

For CRT-P, CARE-HF found a significant reduction in the risk for all-cause mortality compared with OPT (HR = 0.60 [0.47-0.77]; P < 0.0001). In COMPANION, the effect of CRT-P compared with OPT narrowly failed to reach significance (HR = 0.76 [0.58-1.01]; P = 0.059). In MIRACLE the difference between CRT-P and OPT was not statistically significant (HR 0.73 [0.34-1.54; P=0.4)]. Fox *et al*.[34] conducted a meta-analysis of interventions for heart failure in 2007 and concluded that CRT-P conferred a significant benefit compared to OPT in terms of impact on all-cause mortality. This finding has been conformed in a recently published meta-analysis of CRT trials (including RAFT).[96]

CRT-D

For CRT-D, all-cause mortality was analysed in three trials. In COMPANION, CRT-D reduced the risk of death by 36% compared with OPT (HR = 0.64 [0.48-0.86]; P = 0.003). In RAFT, CRT-D significantly reduced mortality compared with ICD (HR = 0.75 [0.62-0.91]; P = 0.003). In MADIT-CRT, there was no significant difference in all-cause mortality between the ICD and CRT-D groups. However, MADIT-CRT was conducted in patients with mild to moderate heart failure whereas the others were conducted in patients with moderate to severe heart failure. Despite not being a formal CRT-D vs. ICD trial, REVERSE reported all-cause mortality rates but not a hazard ratio. Mortality rate was 2.2% in the CRT-ON arm and 1.6% in the CRT-OFF arm (P=0.63).

Fox *et al.*[34] concluded that CRT-D was highly effective in patients with moderate to severe heart failure (risk ratio 0.65 [95% CI 0.49 to 0.85][34]. These findings were again corroborated by the meta-analysis conducted by Wells *et al*.[96]

ICD

All-cause mortality for ICD was compared with OPT in six trials. Three showed a significant reduction with ICD (MADIT, MADIT II and SCD-HeFT), and three did not (AMIOVIRT, CAT and DEFINITE). Notably, ICD reduced all-cause mortality in MADIT and MADIT II, with hazard ratios of 0.46 (0.26-0.82) and 0.66 (0.56-0.78), respectively. Previous meta-analyses have concluded ICD confers significant reduction in mortality compared to OPT (Ezekowitz *et al*. RR 0.72 [95% CI 0.63 to 0.84], Lee *et al*. RR 0.66 [95% CI 0.46 to 0.96].[97;98]

*Table 12: Effect of interventions on all-cause mortality**

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value	Comments
AMIOVIRT				6/51	7/52	NR	0.8	p - value for binary data
CARE-HF			101/409		154/404	0.60 (0.47 -0.77)	< 0.0001	
CAT	5.5 yrs			13/50	17/54	NR*	NR	Cumulative survival after 2, 4 & 6 years of follow up provided 91% ,86%, & 73% in ICD group vs. 93% 80% & 68% in OMT group p=0.554
COMPANION		105/595	131/617		77/308	0.64 (0.48 -0.86) 0.76 (0.58 -1.01)	0.003 0.059	CRT-D vs. OPT CRT-P vs. OPT
Contak-CD	6 months	11/245		16/245		NR	NR	70 additional deaths at long term follow-up reported. However, data were not provided by intervention groups.
DEFINITE				28/229	40/229	0.65 (0.40 -1.06)	0.08	
MADIT				15/95	39/101	0.46 (0.26 - 0.82)	0.009	
MADIT II				NR	NR	0.66 (0.56 - 0.78)	<0.001	Total events reported after 8 years of follow up is 647. However, the data for each arm of treatment were not provided.
MADIT-CRT		74/1089		53/731		1.00 (0.69 -1.44)	0.99	
MIRACLE			12/228		16/225	0.73 (0.34 -1.54)	0.4	
MIRACLE-ICD		14/187		15/182		NR	NR	Cumulative survival at 6 months: CRT-D: 92.4% (95% CI 87.2%-95.3%); ICD: 92.2% (95% CI 87.2%-95.3%). P=0.96
MIRACLE-ICD II		2/85		2/101		NR	NR	
MUSTIC			1/29		2/29	NR	NR	
Piccirillo *et al*		0/16		0/15		NR	NR	
Pinter *et al*		1/36		1/36		NR	NR	
RAFT		186/894		236/904		0.75 (0.62 - 0.91)	0.003	
RESPOND			6/29		10/31	NR	NS	Median follow up of 677.5days not statistically significant for binary end point

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value	Comments
RETHINQ	6 months	5/87		2/85		NR	NR	COS: CRT-D: 94.2% (95% CI 86.7 to 94.6); ICD: 98.8% (95% CI 91.9 to 99.8) P = 0.11.
REVERSE		9/419		3/191		NR	NR	Data for mortality rate reported (CRT-D: 2.2%; ICD: 1.6% P=0.63)
Rhythm-ICD		9/119		3/59		NR	NR	
SCD-HeFT				182/829	244/847	0.77 (0.62 - 0.96)	0.007	Trial also had a third arm (amiodarone). HR compared to placebo. Reported hazard ratio and 95% CI for comparison of ICD vs. OPT.
Vector	6 months		1 /59		1/47	NR	NR	

*All entries n/N unless otherwise stated; **NR** = not reported; **NS** = not statistically significant

3.4.2 Sudden cardiac death

The effect of intervention on sudden cardiac death was reported in 14 of the identified trials (Table 13).

CRT-P

Despite containing no direct mechanism for preventing sudden cardiac death, CRT-P was found to significantly reduce the risk of sudden cardiac death in an extension phase of the CARE-HF study when compared with OPT (HR = 0.54 [0.35-0.84]; P = 0.005). However it did not reduce SCD over OPT in COMPANION (HR 1.21 [0.7-2.07]; P=0.5). Given that these trials were of similar size and conducted in similar patient groups, the evidence for some form of residual benefit associated with CRT-P is currently equivocal, although it is important to note that median follow up in CARE-HF was over twice as long as in COMPANION (37 months compared to 16 months) and hence the CARE-HF results may be more reflective of the long term real world treatment effect. The two smaller studies which reported information for this treatment option (MUSTIC and Vector) made no reference to the statistical significance of the results.

CRT-D

A significant effect of CRT-D on sudden cardiac death was reported in COMPANION, where CRT-D reduced the risk by 56% (HR = 0.44 [0.23-0.86]; P = 0.02) compared with OPT.

ICD

ICD therapy significantly reduced the risk of sudden cardiac death versus OPT in the DEFINITE (HR = 0.20 [0.06-0.71]; P = 0.006) and SCD-HeFT (HR= 0.40 [0.27-0.59]; P < 0.001) studies. MADIT II also proved survival benefit of ICD therapy over OPT (HR for all-cause mortality = 0.66 [0.56-0.78]; P <0.001). Although this trial did not report the mode of death, reduction in SCD is the only plausible mechanism. ICD had no significant effect on sudden cardiac death compared with OPT in the small non-ischemic cardiomyopathy AMIOVIRT study. Studies that directly compared ICD and CRT-D treatment did not report the statistical significance of the findings. Previous authors have concluded that in comparison to OPT, ICD is highly effective in preventing SCD (Ezekowitz *et al*. RR 0.37 [95% CI 0.27 to 0.50][97], Lee *et al.* RR 0.34 [95% CI 0.23 to 0.50][98]).

*Table 13: Effect of interventions on sudden cardiac death**

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value	Comments
AMIOVIRT				1/51	2/52	NR	0.7	p-value for binary data
CARE-HF			32/409		54/404	0.54 (0.35- 0.84)	0.005	
COMPANION		17/595	48/617		18/308	0.44 (0.23- 0.86) 1.21 (0.7- 2.07)	0.02 0.5	CRT-D vs. OPT CRT-P vs. OPT
DEFINITE				3/229	14/229	0.20 (0.06 - 0.71)	0.006	Sudden deaths from arrhythmia. Some death classified as non-cardiac could have been due to arrhythmia but there was not enough information to determine the cause of death.
MADIT II**				NR	NR	0.66 (0.56 - 0.78)	<0.001	Mode of death not reported. SCD is assumed as the mechanism. Total events reported after 8 years of follow up is 647. However, the data for each arm of treatment were not provided.
MIRACLE-ICD		3/87		3/182		NR	NR	
MIRACLE-ICD II		NR		NR		NR	NR	Across both treatment groups, three deaths were as a result of cardiac arrest, while one was due to MI.
MUSTIC			1/29		1/29	NR	NR	
Piccirillo *et al*		0/16		0/15		NR	NR	
RETHINQ		0/87		0/85		NR	NR	
REVERSE		0/419		0/191			NR	
SCD-HeFT				37/829	95/847	0.40 (0.27 -0.59)	< 0.001	Sudden death from ventricular tachyarrhythmia. Hazard ratio & p - value refers to ICD vs. OPT only.
Vector	6 months		0/59		1/47	NR	NR	

***** All results n/N unless otherwise stated; ****** Results relates to all-cause mortality and not specifically to sudden cardiac death; **NR** = not reported;

3.4.3 Death due to heart failure

The effect of intervention on death due to heart failure was reported in eleven trials (Table 14).

CRT-P

In the two larger studies undertaken in patients with severe (NYHA III/IV) heart failure, CRT-P significantly reduced the risk of death due to heart failure compared with OPT in CARE-HF (HR = 0.55 [0.37-0.82]; P = 0.003), but the reduction was not statistically significant in COMPANION (HR = 0.71 [0.46-1.09]; P = 0.15). Given that the two studies were of similar, although not identical design, and recruited individuals who were broadly similar in terms of underlying disease status, the difference in benefit of CRT in reducing heart failure deaths between the two studies is likely to be due to the short length of follow up in COMPANION (14-16 months vs. 30+ months in CARE-HF). However, when these two studies were meta-analysed by Fox *et al.*[34] the resulting treatment effect was significant (risk ratio 0.62 [95% CI 0.46 to 0.83]).

CRT-D and ICD

ICD therapy is not a treatment modality which improves heart function and therefore did not significantly affect the risk of death due to HF compared with OPT in SCD-HeFT. Similarly, there was no significant effect of CRT-D compared with OPT in COMPANION. A previous meta-analysis of ICD vs. OPT in a primary prevention setting conducted prior to the publication of SCD-HeFT concluded that the benefit of ICD on non-arrhythmic death was non-significant (RR 0.95 [95% CI 0.74 to 1.21][98])

*Table 14: Effect of intervention on death due to heart failure**

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value
CARE-HF			38/409		64/404	0.55 (0.37 -0.82)	0.003
COMPANION		52/595	53/617		34/308	0.73 (0.47- 1.11) 0.71 (0.46- 1.09)	0.11 CRT-D vs. OPT 0.15 CRT-P vs. OPT
Contak-CD		NR[1]		NR[1]		NR	NR
DEFINITE				9/229	11/229	NR	NR
MUSTIC			0/29		0/29	NR	NR
Piccirillo et al		0/16		0/15		NR	NR
RAFT		NR[2]		NR[2]			
RESPOND			1[3] /29		9[3] /31	8.41 (1.05 - 67.3)	0.0447
RETHINQ		2/87		2/85		NR[4]	NR[4]
REVERSE			NR[5]	NR[5]		NR	NR
SCD-HeFT				72/829	66/847	1.14 (0.82 -1.60)	NS (ICD vs. OPT only)

***** All results n/N unless otherwise stated; **1** - 47 patients in the trial died due to heart failure during the study treatment and long term follow up phase. This finding was not reported for each intervention group;**2**- One patient died from worsening HF in the ICD group 24 hours after device implantation;**3**- Death due to heart failure after a median follow up of 677.5 days; **4**- Cumulative freedom from death due to worsening HF: CRT - D = 97.7% (91.1 to 99.4) vs. ICD = 98.8% (91.9 to 99.8) p=0.58; **5**- Cause of death not reported by intervention groups. However 3 deaths were adjudicated to be due to progressive HF.**NR** – Not reported **NS** - not statistically significant

3.5 Heart failure related hospitalisations

Twelve trials reported the effect of intervention on incidence or risk of hospitalisation (Table 15). Measures of statistical significance were reported for six of these studies and estimates of the magnitude of any treatment effect in two (CARE-HF and MIRACLE). Discussion on the relative efficacy of the interventions on hospitalisation is therefore somewhat limited.

Compared with OPT, CRT-P significantly reduced the incidence of hospitalisation in CARE-HF (HR = 0.48 [0.36-0.64]; P < 0.001), COMPANION (P = 0.02), MIRACLE (HR = 0.50 [0.28-0.88]; P = 0.02) and MUSTIC (P < 0.056).

CRT-D significantly reduced the incidence of hospitalisation compared with OPT in COMPANION (P = 0.03) and compared with ICD in RAFT (P<0.001) and REVERSE (P=0.03).

In their 2005 systematic review of the primary prevention literature undertaken on behalf of NICE, Bryant *et al*.[99] did not identify any meta-analyses reporting the results for this end point. In contrast, regardless of whether or not the information was reported as risk ratios or rate ratios, Fox *et al.*[34] concluded that CRT-P was effective in terms of significantly reducing heart failure hospitalisations compared to OPT (risk ratio 0.48 [95% CI 0.37 to 0.61], rate ratio 0.60 [95% CI 0.47 to 0.65]).

*Table 15: Effect of intervention on incidence of hospitalisation**

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio(95% CI)	P-value
CARE-HF			72[1]/409		133[1]/404	0.48 (0.36 -0.64)[1]	< 0.001
COMPANION		372/595	388/617		199/308	NR	0.03 CRT-D vs. OPT 0.02 CRT-P vs. OPT
Contak-CD		32[2] /245		39[2] /245		NR	0.352
MADIT II				148[3] /742	73[3]/490	NR	NR
MADIT-CRT		136[4]/1089		140[4]/731		NR	0.59[10]
MIRACLE			18/228[5]		34/225[5]	0.50 (0.28 -0.88)[5]	0.02
MIRACLE-ICD		85/187		78/182		NR	NR
MUSTIC			3[6]/29		9[6] /29	NR	< 0.056
Piccirillo *et al*		0/16		2[7] /15		NR	NR
Pinter *et al*		11/36		13/36		NR	NR
RAFT		174[8] /894		236[8] /904		0.68[8]	<0.001
REVERSE		17[9] /419		15[9] /191		0.47[9]	0.03

***** All results n/N unless otherwise stated**; *1***- These data refers to a mean FU of 29.4 months from unplanned hospitalisation with worsening HF; **2**- The data and p- value reported refers to the number of patients with at least one hospitalisation due to progression of HF; **3**- These data refers to patient hospitalised with HF, mean follow-up 20 months; **4-** Refers to only patients who had heart failure event during hospitalisation; **5**- Hospitalisation due to heart failure; **6**- Data refers to number of hospitalisations analysed in the first period (first 12 weeks) only; **7**- Hospitalisation due to worsening HF; **8**- The hazard ratio and P value reported in the table represent patients who were hospitalised for heart failure. A total of 1018 patients were hospitalised at least once during follow up; 509 in each treatment arm. The majority of this hospitalisation was for cardiovascular reasons. A total of 404 in the ICD group and 423 in the CRT-D group were hospitalised for a cardiac cause [HR = 1.04,p -value = 0.56] in the CRT-D & ICD group respectively.; **9**- Hospitalisation due to HF. Hazard ratio not reported except for time to first hospitalisation due to HF as can be seen in the table. No data reported for CRT -P vs. OPT.*;* **10 -**Study used “heart failure events” definition that required intravenous drug therapy for outpatient events or proof of decongestive therapy for inpatients.

3.6 Other clinical end points

3.6.1 Change in NYHA class

Change in NYHA class was reported in 11 studies, and was reported and analysed using a variety of different end points (Table 16 to Table 19).

CRT-P

CRT-P was associated with improvements in NYHA class outcomes versus OPT in all trials where these outcomes were reported. CRT-P was associated with a significantly lower mean NYHA class than OPT after 90 days (2.1 versus 2.7, difference in means = 0.6 [0.4-0.7]; P = 0.001) in CARE-HF. In RESPOND, there was a significant reduction in mean NYHA class from baseline with CRT-P compared with OPT (3.34 to 2.24; P = 0.0001). In COMPANION, 61% of patients receiving CRT-P had improved NYHA class at 6 months, compared with 38% on OPT (P < 0.001). In MIRACLE, 52% and 16% of patients treated with CRT-P improved by at least one and at least two NYHA classes, respectively, compared with 32% and 6%, respectively, with OPT (P < 0.001).

CRT-D and ICD

CRT-D was associated with significant improvements in NYHA end points over ICD alone in four out of five trials where this was reported. CRT-D was compared with OPT in one trial, COMPANION: 57% of patients with CRT-D had improved their NYHA class at 6 months, compared with 38% on OPT (P = 0.001).

In MIRACLE ICD, patients with ICD whose CRT was turned on had a mean improvement in NYHA class of one, whereas patients with ICD whose CRT was turned off showed no change (P = 0.007). In MIRACLE ICD II, which included only patients with NYHA class II, improvement in NYHA class from baseline was greater (difference: -0.18) in patients with CRT activated compared with CRT off (difference: 0.01; P = 0.05).In Rhythm-ICD, the mean change in NYHA class from baseline was -0.48 with CRT-D and -0.28 with ICD (P = 0.048).

In RETHINQ, 54% of patients with CRT-D had improved by at least one NYHA class, compared with 29% of those with ICD (P = 0.006). In Contak CD, there was no difference in NYHA class outcome between CRT-D and ICD.

Table 16:NYHA class, mean (SD) value at 90 days

	CRT-P (N=409)	OPT (N=404)	Difference in means (95% CI)	P value
CARE-HF	2.1 (1.0)	2.7 (0.9)	0.6 (0.4 to 0.7)	<0.001

Table 17:NYHA at baseline and six months (mean, SD)

	CRT-P		P value	OPT		P value
	Baseline	6 months		Baseline	6 months	
RESPOND	3.34 (0.48)	2.24 (0.99)	p<0.0001	3.12 (0.43)	3.32 (0.79)	NR

Table 18: Change in NYHA class, number of pts (%) at 6 months (CRT-P and OMT only)

Miracle	CRT-P (n=213)	OPT (n=193)	P Value
Improved by two or more classes	34 (16)	12 (6)	<0.001
Improved by one class	109 (52)	62 (32)	
No change	64 (30)	115 (59)	
Worsened	4 (2)	7 (4)	

Table 19: Change in NYHA class , number of pts. (%) (CRT-D and ICD only)

RETHINQ	CRT-D (n=76)	ICD (n=80)	P value
Improved by one class or more	41 (54)	23 (29)	0.006
No Change	31 (41)	51 (64)	
Worsened	4 (5)	6 (8)	

Table 20: Change in NYHA class, number of pts. (CRT-D and ICD only)

Contak-CD	CRT-D	ICD	P Value
All patients (CRT-D N=109, ICD N=116)			
Improved two classes	11	2	0.10
Improved one class	25	30	
No change	51	51	
Worsened	13	17	
NYHA Class III/IV at randomisation (CRT=D N=45, ICD N=48)			
Improved two classes	27	4	0.006
Improved one class	47	50	
No change	22	38	
Worsened	4	8	
NYHA Class I/II at randomisation (CRT=D N=64, ICD N=68)			
Improved two classes	-	-	0.84
Improved one class	9	16	
No change	72	60	
Worsened	19	24	

Table 21: Improvement at 6 months in NYHA class symptoms (%)

	CRT-D (n=497)	CRT-P (n=489)	OPT (n=199)	P value
COMPANION	57	61	38	P<0.001 (CRT-P vs. OPT) P<0.001 (CRT-D vs. OPT)

Table 22: Change in NYHA class - baseline and 6 months (median, 95% CI)

	CRT-D (n=165)	ICD (n=162)	P value
MIRACLE-ICD	-1(-1 to -1)	0(-1 to 0)	0.007

Table 23: Change in NYHA class - baseline and 6 months (mean, SD)

	CRT-D		ICD		
	No. of patients	value	No. of patients	value	P value
MIRACLE-ICD II	82	-0.18(0.61)	98	0.01 (0.63)	0.05
Rhythm-ICD	83	-0.48 (0.65)	43	-0.28 (0.63)	0.048

Table 24: Percentage of patients that worsened/improved NYHA at 12 months

REVERSE	CRT-D (n=419)	ICD (n=191)	P Value
Worsened	10	9	NR
Improved	14	15	NR

Table 25: NYHA class distribution after one year of treatment (number of pts)

	ICD		CRT-D	
Piccirillo *et al.*	**Baseline**	**One year**	**Baseline**	**One year**
NYHA class, I	0	0	0	1
NYHA class, II	0	1	0	1
NYHA class, III	5	1	5	6
NYHA class, IV	10	13	11	6

3.6.2 Change in LVEF

The effect of intervention on change in LVEF from baseline was reported in 14 studies (Table 26).

CRT-P

In MIRACLE, patients in the CRT-P arm had a mean increase in LVEF of +4.6%, compared with a mean reduction of 0.2% with OPT (P < 0.001). At 18 months of follow up, CARE-HF noted a difference in mean LVEF of +6.9% ([5.6 – 8.1] P = <0.001) between the CRT-P arm and the OPT arm. However, there was no significant difference between CRT-P and OPT in terms of LVEF change in RESPOND.

CRT-D versus ICD

CRT-D was associated with significantly greater LVEF improvement compared with ICD in Contak-CD (all patients; P=0.02 and those with NYHA class III or IV; P=0.029 difference in patients with NYHA class I or II was not significant); in

MIRACLE-ICD II (3.8% with CRT-D versus 0.8% for ICD, P = 0.02); and in REVERSE (mean LVEF at 12 months 31.8% and 27.0% with CRT-D and ICD respectively; P for change from baseline < 0.01). In MADIT-CRT, LVEF change was 11% with CRT-D and 3% with ICD only (P = 0.0001).

There was no significant difference in LVEF outcome between CRT-D and ICD in MIRACLE ICD, Pinter *et al*. or RETHINQ.

Table 26: Effect of intervention on change in LVEF

Study	Time point	CRT-D	CRT-P	ICD	OPT	P-value	Comments
CARE-HF	18 months		NR		NR	< 0.001	Difference in means (95% CI) +6.9 (5.6 to 8.1)
Contak-CD (all patients)		5.1 (0.7)[a]		2.8 (0.7)[a]		0.02	
Contak-CD (NYHA I/II)		4.7 (0.9)[a]		2.9 (0.9)[a]		0.16	
Contak-CD (NYHA III/IV)		6.0 (1.1)[a]		2.3 (1.2)[a]		0.029	
MADIT-CRT	12 months	11[d] (0.05)[a]		3[d] (0.03)[a]		0.0001	
MIRACLE			+4.6 (+3.2 to +6.4) [b]		-0.2 (-1.0 to +1.5)[b]	< 0.001	
MIRACLE-ICD	6 months	2.1 (1.2 to 4.1)[b]		1.7 (0.7 to 2.4)[b]		0.12	
MIRACLE-ICD II	6 months	3.8 (8.0)[a]		0.8 (6.2)[a]		0.02	
Piccirillo et al	12 months	Baseline: 23 (4)[a] Study end: 28 (4)[a]		Baseline: 22 (8)[a] Study end: 22 (8)[a]		ICD arm NS, CRT-D arm <0.05	
Pinter et al	6 months	3.9 (8.9)[a]		1.9 (6.8)[a]		NS	
RESPOND			6.72 (18.4) [c]		5.37 (10.4)[c]	0.7533	
RETHINQ		1.2 (-0.4 to 4.4)[b]		2.0 (0.3 to 4.2)[b]		0.83	
REVERSE	12 months	Baseline: 27.2 (6.6)[a] Study end: 31.8 (8.8)[a]		Baseline: 26.4 (6.7)[a] Study end: 27.0 (7.1)[a]		< 0.01	
Rhythm-ICD	6 months	4.3 (9.9)[a]		2.9 (6.2)[a]		NR	

a - mean (SD); **b**- median (95% confidence interval); **c**- median (interquartile range); **d** – (percentage)

3.6.3 Incidence of ventricular tachycardia/ventricular fibrillation (VT/VF)

Cross-study interpretation of results is difficult due to the lack of consistent reporting (Table 27). Nonetheless, some general points arise.

It has been proposed that CRT may prevent ventricular arrhythmias[83]. The only trials to report a statistical analysis of the rates of VT/VF incidence between treatment arms were CONTAK-CD, MIRACLE ICD, MIRACLE ICD II and REVERSE. All compared the incidence of spontaneous VT or VF in patients on CRT-D versus ICD, and all found no significant difference between the two.

Table 27: Effect of intervention on incidence of VT/VF (n/N)

Study	CRT-D	CRT-P	ICD	OPT	P-value	Comments
AMIOVIRT			18/51	2/52	NR	In ICD group, this refers to 16 patients who received appropriate therapy for VA and 2 patients who had syncope due to VT. While in OPT, 2 patients had an ICD implanted due to documented VT
CAT			17/50	NR	NR	Refers to 11 patients who received adequate therapy for VTs > 200bpm, and 6 patients who had syncope during VT
Contak-CD	36/245		39/245		NS	Those patients in the CRT-D group who experienced VT/VF had a median of 2.5 episodes while those in the ICD group had a median of 2 episodes.
DEFINITE			NR	NR	NR	Three and fourteen patients in the ICD and OPT group had arrhythmia. Type was not specified
MADIT II			NR	21/490		Twenty one patients received a defibrillator for documented or suspected malignant VA
MIRACLE-ICD	42/187		47/182		0.47	Pertains to patients who experienced at least one episode of ventricular tachycardia or fibrillation.
MIRACLE-ICD II	19/85		26/101		0.61	Related to individuals who experienced at least one appropriately detected, spontaneous episode of VT/VF
Piccirillo *et al*	2/16		4/15		NR	Individuals receiving appropriate ICD shocks for sustained VT/ VF
Pinter *et al*	7/36		6/36		NS	Number of patient requiring therapy from their device.
RESPOND		NR/29		1/31	NR	One patient in the OMT group crossover to the CRT-P with defibrillator backup after development of a sustained ventricular tachycardia
REVERSE	54/345		24/163		0.09	There were 196 and 114 adjudicated episodes of VT/ VF in the CRT-D and ICD group respectively. Of note, the non-significant difference is likely to have arisen due to the 2:1 randomisation mechanism.
SCD-HeFT			177/829	95/847	NR	The number of individuals who had VT/VF in the OPT group could be more than the reported number.. The figure reported here refers to incidence of ventricular tachyarrhythmia leading to sudden death. In the ICD group, it refers to those who received shocks from their device for rapid VT/VF

NS - not statistically significant; **NR**- Not Reported

3.7 Health related quality of life

3.7.1 EQ-5D

Three trials collected HRQoL data using the EQ-5D instrument. Data from two of these (RAFT and MADIT-CRT) is not yet in the public domain. These data are re-discussed in the section on the IPD analysis relating to the modelling of HRQoL. Mean EQ-5D scores from CARE-HF are shown in Table 28. Patients receiving CRT-P reported significantly higher scores than those on OPT (mean difference (95% CI) 0.13 (0.08, 0.18) $p < 0.0001$). This size of difference is generally considered highly clinically significant with EQ-5D.

Table 28: Health related quality of life: EQ-5D instrument (mean (95% CI))

Study	Time point	CRT-D	CRT-P	ICD	OPT	P-value	Comments
CARE-HF	3 months		0.56 (0.52-0.59)		0.43 (0.39-0.46)	< .0001	Mean difference (95% CI) 0.13 (0.08, 0.18)

3.7.2 Change in MLWHF

Information on health related quality of life was also collected using the Minnesota Living With Heart Failure (MLWHF) instrument. While not a direct representation of the utility associated with different treatment/disease severity combinations, these data are informative as to the likely benefit of treatment on HRQoL, and hence can be used to both infer utility and to validate the results from the IPD analyses.

At six months, individuals in the COMPANION clinical trial[51] with either a CRT-P or CRT-D reported an approximate 25% improvement in MLWHF ($p<0.001$ compared to OPT). Similar impressive results were observed in the active treatment arms of the MIRACLE and MIRACLE-ICD trials (absolute changes of -18 and -13.3% respectively). Thus, CRT has a strong impact on an individual's HRQoL, and the results for CRT-D from the smaller clinical trials support this conclusion.

Information on the impact of ICD on MLWHF scores was available from ten studies. Young *et al*.[83] analysed data using two different methods and reported a significant improvement associated with ICD treatment in both (absolute change =-11). This change was also significantly less than observed for CRT-D. In contrast, Abraham *et al.* [44] reported a similar improvement (-10.7) but the result was not significantly different to that observed for CRT-D. It is important to note, however, that the two studies were undertaken in different patient groups and may not be directly comparable.

Higgins *et al.*[60] reported the results from the CONTAK-CD (change in MLWHF scores) by all patients and by disease severity (NYHA I/II and III/IV). This study is thus informative in assessing the impact of treatment in different patient groups. While there was no significant difference between the two treatments in the overall group ($p=0.39$), when the results for each subgroup are assessed the impact of treatment is significant in the more severely ill patients ($p=0.017$) and not in the less severely ill ($p=0.26$).

Table 29: Absolute MLWHF scores by study

Study	Time point	CRT-D	CRT-P	ICD	OPT	P- value	Comments
CARE-HF	End of study		27.2 (24.9-29.5)		35.1 (32.6-37.6)	< 0.0001	Mean (95% CI). Individuals who died were not included in the analysis. Mean difference (95%CI) -10.1 (-6.8 -13.3)
MUSTIC	3 months		29.6 (21.3)*		43.2 (22.8)	< 0.001	Mean (SD). Data analyzed amongst 45 patients in the CRT-P and OPT group.
RESPOND	6 months		44.6 (30.0)*		62.1(27.7)*	0.0265	Mean (SD)

*Table 30: Effect of intervention on change in MLWHF scores**

Study	Time point	CRT-D	CRT-P	ICD	OPT	P- value	Comments
COMPANION	6 months	-26% (28)	-25%(26)		-12% (23)	<0.001 <0.001	CRT-D vs. OPT ICD vs. OPT
Contak-CD (all patients)		-7 (2)		-5 (2)		0.39	
Contak-CD (NYHA I/II)		-1 (2)		-4 (2)		0.26	
Contak-CD (NYHA III/IV)		-16 (3)		-5 (3)		0.017	
MIRACLE	6 months		-18 (-22 to -12)		-9 (-12 to -5)	0.001	median (95% CI)
MIRACLE-ICD	6 months	-17.5 (-21 to -14)		-11 (-16 to -7)		0.02	median (95% CI)
MIRACLE-ICD II	6 months	-13.3 (25.1)		-10.7 (21.7)		0.49	
Pinter *et al*	6 months	-7.8 (20.1)*		-0.2 (13.5)*		NS	
RETHINQ	6 months	-8 (-10 to -1)		-7 (-11 to 3)		0.91	median(95% CI)
REVERSE	12 months	-8.4 (17.1)		-6.7 (15.9)		0.26	
Rhythm-ICD	6 months	-7.8 (22)		+3.4 (31)		0.009	

* All results mean (SD) unless otherwise stated; NS – Not significant

Table 31: Effect of intervention: change in MLWHF dimension scores (mean (SD))

Study	Time point	CRT-D	CRT-P	ICD	OPT	P- value	Comments
DEFINITE	Approx. 3 month			ES: -0.8 (0.1) PS: -1.5 (0.2);	ES: -0.7 (0.1); PS: -1.6 (0.2);	NS in long term HRQL	After 3 months, emotional score remained stable in both groups and physical scores decreased in both groups

3.8 Device- and procedure-related adverse events

All trials except one (RESPOND) collected and reported adverse events data. Due to differences in the methods of reporting it is difficult to directly compare and/or summarise the findings of the various trials. Adverse events reported in the trials are presented in detail in Appendix 5. Here we present a brief narrative overview, including information from previous meta-analyses.

CRT-P and CRT-D

In the five RCTs assessed for TA120 (CARE-HF, COMPANION, MIRACLE, MUSTIC-SR, CONTAK-SD), the estimated rate of perioperative death associated with CRT (CRT-P and CRT-D pooled) was 0.8% (95% CI 0.5% to 1.2 %). CRT devices were implanted successfully on average in 90.8% of patients (95% CI 89.6% to 92.0%).[100] The most common causes of implant failure were related to the placement of the left ventricle (LV) lead, and the most common postoperative event was lead dislodgement. The COMPANION trial reported no significant difference in the rate of device- and surgery-related adverse events between CRT-P (10% compared with optimal pharmacological therapy) and CRT-D (8% compared with optimal pharmacological therapy). In COMPANION, 69%, 66% and 61% of patients in the CRT-D, CRT-P and OPT arm respectively experienced moderate to severe adverse events from any cause (including those arising from patients' underlying condition).

In REVERSE there was a 97% overall implantation success rate, with 26 peri-procedural complications among the 642 patients (4%) who underwent an implant attempt. After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients (16%) experienced a total of 138 procedure or system-related complications. One complication resulted in death. After implantation, and during the 24-month follow-up, 26 of the 262 successfully implanted patients experienced a total of 30 device-related serious adverse events (SAEs). The percentage of patients with SAEs in the CRT-ON versus CRT-OFF study groups were similar (P=0.66). At the time of study closure, 29 of the 30 post-implant, device-related serious adverse events were resolved. Because most patients in REVERSE had a primary prevention indication for an ICD, the added risk of implanting a CRT device was related to the LV lead. This

risk was relatively low, with an LV lead-related complication rate of 10% over the 12 months for the complete study population.

ICD and CRT-D

Serious adverse events due to ICDs were reported infrequently in the trials assessed for TA95[33] Recorded complications included infection, haematomas and bleeding, lead dislodgement and migration, cardiac perforation, pleural effusion and pneumothorax, and device dysfunction/malfunction of the generator.

In RAFT, during the first 30 days after device implantation, there were 13.3% device or implantation related complications among patients in the CRT-D group and 6.8% patients in the ICD group. The number of device-related hospitalisations over the entire study period was higher in the CRT-D group (20.0%), as compared with in the ICD group (12.2%). One death from worsening HF occurred in the ICD group within 24 hours of device implantation.

In MADIT-CRT there was successful implantation of a device in 98.4% of patients. During long-term follow-up after the first 30 days, serious device-related adverse events occurred with a frequency of 4.5 per 100 device-months in the CRT-D group and of 5.2 per 100 device-months in the ICD-only group. Of 1079 CRT-D patients that were included in the safety end point of MADIT-CRT, 164 patients (15.2%) experienced 214 system-related complications within 90 days post-implant. Left ventricular lead problems following implantation were reported in 4% of patients in a 30-day period. Device related infections occurred in 1% of CRT patients within 30 days of implantation. One death, due to pulmonary embolism, occurred in the CRT-D group.

Peri-implantation mechanical complications, including pneumothorax, coronary dissection, and pericardial tamponade occurred with a 1% frequency in the REVERSE trial, and 2% in MADIT-CRT.

Another problem associated with ICD implantation is inappropriate shock therapy, mostly for atrial fibrillation with rapid ventricular response but also for various other reasons. The occurrence of inappropriate shocks varies across studies in between 0.5 and 19% of patients within 30 days of implantation, and in 14% thereafter.

3.9 Long-term follow-up data on mortality

A major uncertainty in CRT and ICD therapy is the duration of any observed treatment effect on mortality. Long-term follow-up data on mortality from MADIT-II is in the public domain. For CARE-HF, a copy of a manuscript in preparation containing long-term data has been made available. These data are summarised below. Some long-term data from SCD-HeFT were presented at a recent international meeting but relative efficacy estimates (hazard ratios or relative risks) were not presented, so data from this study has not been included here.

3.9.1 CARE-HF

CARE-HF carried out long-term follow-up from 2005 until September 2009. The median potential follow-up, disregarding death or censorship, was 90 months. Median follow-up with censoring for death or loss to follow-up was 50 months in the control group and 56 months in the CRT-P group.[101] Of 813 patients originally enrolled, 558 were alive at the end of the main study and a short post-trial observation phase. For the long-term follow-up, 111 (24% of those not known to be dead) could not be contacted, and 50 (11%) declined to participate. Of patients originally assigned to the control group (OPT), 156 were known to have received CRT during or after the trial.

In all, 222 patients in the OPT group and 192 patients assigned to CRT-P were known to have died since randomisation. The hazard ratio for death in patients originally randomised to CRT compared to those randomised to OPT was 0.768 (95% CI 0.633 to 0.931; P = 0.007). At five years, mortality was 43.9% in the original OPT group compared to 32.2% in those assigned to CRT. At 6.5 years mortality was 56.3% and 49.1% respectively, and at eight years mortality was 61.8% and 54.8%. The greatest divergence between the survival curves was at 3 years. No significant differences between patient subgroups were found, except that patients below the median age at randomisation survived longer. Patients assigned to CRT had a more favourable outcome regardless of age.

Therefore, a highly clinically significant survival benefit for original treatment with CRT persisted at a median of 50-56 months from randomisation and beyond, despite the fact that almost all surviving patients in the OPT group received CRT after the study.

3.9.2 MADIT II

An 8-year follow-up study was published of MADIT II.[102] During the 3.5-year period of the study, ICD was associated with an average survival gain of only 0.167 years (2 months). Information on post-trial mortality as of September 2009 was obtained for all patients in the study (median follow-up 7.6 years, total follow-up of 7815 patient-years).

Of the 742 patients randomised to ICD, 22 patients did not receive an ICD and 13 had the ICD extracted during the trial. In the medical therapy arm (n=490), 27 patients crossed over to the ICD arm during the trial, and 140 received an ICD within 4 months after trial closure. Fewer than 5% of patients are thought to have crossed between treatment arms during the subsequent follow-up.

At 8 years of follow-up, all-cause mortality was 49% among patients treated with an ICD compared with 62% among non-ICD patients (P<0.001). Multivariate analysis showed that ICD was associated with a significant long-term survival benefit (HR for 0- to 8-year mortality=0.66 [95% CI 0.56 to 0.78]; P<0.001). ICD was found to be associated with a significant reduction in the risk of death at up to four years (HR =0.61 [95% CI 0.50 to 0.76]; P<0.001), and with a continued survival benefit from 5 to 8 years (HR =0.74 [95%CI 0.57 to 0.96]; P=0.02).

These findings demonstrate a sustained 8-year survival benefit with primary ICD therapy in the MADIT-II population.

4 Analysis of individual patient level data

- We carried out a meta-analysis of individual patient level data (IPD) from 13 clinical trials (12,638 patients, followed up for up to 7.5 years) – the first such analysis ever undertaken in CRT/ICD therapy.
- We believe that the power of the IPD approach means these are the best and most robust data available on the treatment effects of CRT and ICD devices in the different subgroups of patients with heart failure.

All-cause mortality

- The objective of the mortality analysis is to understand how the use of CRT-P, ICD, and CRT-D impact on the overall survival (OS) curve of different patient groups eligible for these devices.
- Synthesising IPD as opposed to aggregating published data is necessary in order to capture the differences in baseline risk and relative treatment effects across the highly heterogeneous patient population eligible for these devices.
- A baseline risk analysis was conducted in order to predict mortality risk over time for patients receiving OMT (3,477 patients, followed up for up to up to 6.1 years). This analysis found NYHA class, ischaemia, QRS duration and left ventricular ejection fraction (LVEF) all to be highly significant predictors of survival times, along with patient age and gender.
- The aim of the network meta-analysis was to estimate the relative treatment effects comparing each device to the other devices, and to OMT.
- Details of methods and analyses are presented.
- The network meta-analysis found CRT-D to have the strongest effect on all-cause mortality, with a hazard ratio of [redacted]
- Age, gender and QRS morphology (both QRS duration and LBBB status) were found to be independently predictive of the magnitude of benefit associated with the devices. The impact of QRS duration and LBBB is attributable to CRT.

- A summary of key findings on the treatment effects of each device type on all-cause mortality for different patient subgroups is given in Section 4.6.2

All cause hospitalisation

- For the base case, hospitalisation was modelled as number of events per month; a days per month approach was also performed as a sensitivity analysis. Hospitalisation rate in patients receiving OMT only was taken as the baseline rate.
- Treatment effects on hospitalisation rate were derived for each device in each NYHA class (NYHA I/II were pooled). These were used to create probabilities for use in the economic model.
- Across all NYHA classes, device therapy was associated with a reduction in admission rates.
- In NYHA classes I to III, ICD was associated with a [redacted] reduction in monthly admission rates, and CRT with a [redacted] reduction.
- The effect in NYHA class IV was even more pronounced, with CRT offering a [redacted] reduction in monthly admission rates.

Health Related Quality of Life

- As noted in Section 3.7, individual studies showed significant HRQoL improvements for devices, compared to baseline regardless of instrument used. The primary HRQoL analysis used EQ-5D data only. Potential mapping approaches using MLWHF data were not possible due to the absence of an algorithm.
- For ICD based treatment in NYHA classes I/II, improvement in MLWHF existed for approximately [redacted] years. In NYHA classes III/IV, the duration of benefit was approximately [redacted] years.
- After accounting for placebo effects, CRT had a strong impact on HRQoL [redacted] in NYHA classes I/II; [redacted] in NYHA classes III/IV).
- There was also a small positive impact of ICD therapy in patients with NYHA classes I/II [redacted], but not for patients with NYHA classes III/IV (hence any extension of life in these patients will have the same HRQoL as would be observed on OPT).

4.1 Introduction

As part of the joint submission, individual patient data from 12,638 patients recruited into 13 clinical trials were made available for the purpose of model construction.[8;43;44;47;49;51;54;60;64;67;79;80;83] This is the first network meta-analysis of individual patient data ever conducted in the field of CRT/ICD devices, and as such represents a powerful tool for generating new insights into this major body of clinical data. It was made possible by the decision of all the major device manufacturers to make available their proprietary data, in the interests of obtaining the best possible information on the treatment effects and cost-effectiveness of the three device classes in different subgroups of the heterogeneous population of patients who have heart failure.

The analysis was a major undertaking, and such an approach would not be warranted for the majority of health technology assessments. However, it was felt that the nature of the evidence and the value of the information to be gained justified the resources needed. In particular, the high degree of patient heterogeneity inherent in heart failure (such as the wide difference between patients in NYHA class I and class IV) is a strong indicator for an individual patient data approach[103].

The IPD analysis aimed both to confirm the existing evidence and to address previously unanswered questions. In particular, we hoped to gain new insight into:

- What is the risk of death over time in different patients groups?
- What is the relative efficacy of each intervention compared to OMT in terms of all-cause mortality reduction, and does this differ by patient group?
- How does health related quality of life vary by device and patient group?
- How does the rate of all cause hospitalisation vary by device and patient group?

The analyses of each of these three categories are discussed separately below.

4.2 Mortality

4.2.1 Objective

The objective of the individual patient data (IPD) mortality analysis is to understand how the use of CRT-P, ICD, and CRT-D impact on the overall survival (OS) curve for different patient groups receiving these devices.

Synthesising IPD as opposed to aggregating published data is necessary in order to capture the differences in baseline risk and relative treatment effects across the highly heterogeneous patient population receiving these devices. This would not have been possible using published subgroup data: subgroup analyses were not consistently reported across trials, and even where available would not have allowed a multivariate analysis to be performed. A multivariate analysis is necessary to simultaneously assess the impact of each characteristic of a presenting patient on their expected outcome.

Previous NICE guidance and other guidelines have made recommendations regarding use of the devices in specific subpopulations based on the inclusion criteria of individual trials and reported subgroup analyses. The availability of IPD allows for a more formal synthesis of these data, in their entirety, rather than relying on a more informal qualitative synthesis of the available data. This is particularly important in the context of cost-effectiveness analysis, where it is important to not only understand which patient characteristics impact on outcomes, but to estimate the magnitude of impact of different patient characteristics.

4.2.2 Terminology

The following terminology is used throughout the discussion of the mortality analysis:

- Baseline risk – the risk of mortality for patients receiving OMT (optimal medical therapy; also referred to elsewhere as OPT).
- Treatment effect – the impact (relative to OMT) of device implantation (ICD, CRT-P or CRT-D) on mortality as measured on the hazard ratio scale.
- Covariable – a patient characteristic known at baseline that is expected to impact on either the baseline risk of mortality, the treatment effect of a device

on mortality or both.

- Baseline-risk modifier – a covariable that alters the risk of death for patients receiving OMT.
- Treatment effect modifier – a covariable that alters the hazard ratio for a device compared to OMT.

4.3 Overview of methods

4.3.1 Data

4.3.1.1 Network of evidence

All trials identified by the systematic review (see Section 3) were considered for inclusion in the network meta-analysis. The network of evidence formed by these trials is presented as Figure 12. All trials compared two devices with the exception of COMPANION which compared CRT-D, CRT-P and OMT.

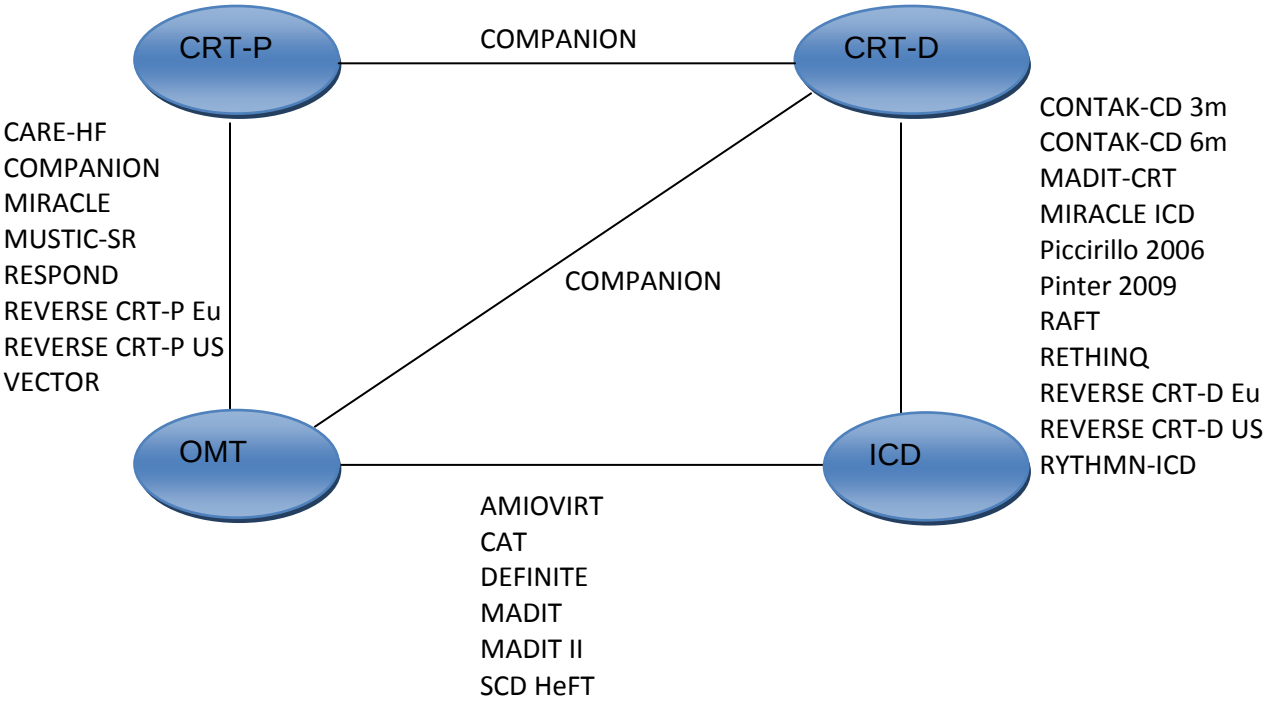
The following trial-specific study design issues should be noted when interpreting the figure:

- CONTAK-CD enrolled patients into two study designs (phases). In both study designs all patients received a CRT-D device and were randomised to CRT 'on' or CRT 'off'. Patients were initially enrolled in to a cross-over design with patients crossing over to CRT 'on' or 'off' at three months (Phase 1). However, part-way through the trial patients were enrolled into a six month parallel group trial (Phase 2). As CONTAK-CD was therefore effectively two different trials, these are included separately in the network meta-analysis as CONTAK-CD Ph 1 and CONTAK-CD Ph 2.
- MIRACLE ICD and MIRACLE ICD II, although reported in separate publications, actually describe a single trial. This is therefore labelled as MIRACLE ICD and considered as a single trial in the analysis.
- The REVERSE trial allowed physicians to select a CRT-P or CRT-D device. Patients were then randomised to CRT-ON or CRT-OFF. As the trial did not randomise patients across the four therapies they received (OMT, CRT-P, ICD, CRT-D) there is effectively a "REVERSE CRT-D" and a "REVERSE CRT-P" trial. This trial is further split in to European (EU) and US trials for the analysis due to the different protocol-specified durations of follow-up in these

geographies (24 months and 12 months respectively). There are therefore effectively four REVERSE trials in the analysis “REVERSE CRT-D US”, ”REVERSE CRT-D EU”, ”REVERSE CRT-P US”, ”REVERSE CRT-P EU”.

- The SCD HeFT trial randomised patients to three arms: conventional therapy plus placebo; conventional therapy plus amiodarone and conventional therapy plus ICD. Based on clinical advice and the all-cause mortality endpoint results from this study (amiodarone vs. placebo hazard ratio 1.06 (95% CI 0.86-1.30)) the amiodarone and placebo arms of this trial are pooled in the analysis.

Figure 12: Network of randomised controlled trials



As documented in the systematic review, the trials included were first reported between 1996 (MADIT) and 2010 (RAFT). Clinical experts were consulted to ascertain whether the devices were likely to have changed during this period in a way that would modify the relative treatment effects. The clinical experts indicated that the impact of the devices on mortality was unlikely to have changed over this period. The main technological advances have increased procedural success rates and device longevity, and reduced inappropriate shocks associated with ICD therapy.

4.3.2 Availability of IPD

We obtained IPD from 13 of the 22 trials identified by the systematic review. Data

were requested from the device manufacturers using a standardised data sheet. Boston Scientific provided data from the following trials: COMPANION, CONTAK-CD, MADIT, MADIT II; and MADIT-CRT. Medtronic provided data from: CARE-HF, MIRACLE, MIRACLE-ICD, RAFT, REVERSE, and SCD-HeFT. St. Jude Medical provided data from DEFINITE and RethinQ.

The IPD trials include 95% of the total number of patients included in the network. This reflects the fact that the trials for which IPD were not available were relatively small (see Table 32).

Table 32 describes the numbers of patients included in the analysis for each trial. These replicate the primary analyses of each trial.

The data set including the 22 trials identified by the systematic review is referred to as the 'All Trials' data set. The data set including trials for which IPD were available is referred to as the 'IPD Trials' data set.

The reasons for IPD not being available are documented below:

- CAT, Piccarillo *et al*. – these trials were not sponsored by manufacturers contributing to this submission (the former was funded by the University of Michigan and the latter's funding was not stated).
- AMIOVIRT, MUSTIC-SR, Pinter *et al*., RHYTHM-ICD- these studies were sponsored by the submitting manufacturers (Boston Scientific, Medtronic, Guidant Corporation (part of Boston Scientific) and St Jude Medical, respectively). However, the data were not included in the analysis as they were not available (AMIOVIRT, Pinter *et al.*), or the available IPD databases were not thought to be of sufficiently reliable quality for inclusion (MUSTIC-SR, RHYTHM-ICD), where in both cases the available data sets could not be reconciled with the published data.
- VECTOR and RESPOND - the systematic review did not identify the studies until after the database had been assembled and it was not therefore feasible to include these studies in the IPD in the analysis.

Despite the unavailability of individual patient data from these studies, as shown in Table 32 the IPD contains 95% of the patients included in the RCT evidence base.

Table 32: Trials included in network meta-analysis - IPD availability

Trial / Device	CRT-D	CRT-P	ICD	OMT	Total
IPD available (number of patients)					
CARE-HF [8]	0	409	0	404	813
COMPANION [51]	595	617	0	308	1,520
CONTAK_CD ph1 [60]	111	0	104	0	215
CONTAK_CD ph2 [60]	134		141	0	275
DEFINITE [62]	0	0	229	229	458
MADIT [68]	0	0	95	101	196
MADIT-CRT[66]	1,089	0	731	0	1,820
MADIT II [71]	0	0	742	490	1,232
MIRACLE [43]	0	228	0	225	453
MIRACLEICD [44]	272	0	283	0	555
RAFT [80]	894	0	904	0	1,798
RethinQ[49]	87	0	85	0	172
REVERSE CRT-D US [64]	227	0	104	0	331
REVERSE CRT-D Eu[64]	118	0	59	0	177
REVERSE CRT-P US [64]	0	12	0	5	17
REVERSE CRT-P Eu[64]	0	62	0	23	85
SCD-HeFT[48]	0	0	829	1,692	2,521
Total	**3,527**	**1,328**	**4,306**	**3,477**	**12,638**
IPD Not available (number of patients)					
AMIOVIRT [79]	0	0	51	52	103
CAT [47]	0	0	50	54	104
MUSTIC-SR [54]	0	29	0	29	58
Piccirillo 2006 [74]	16	0	15	0	31
Pinter 2009 [75]	36	0	36	0	72
RESPOND [59]	0	29	0	31	60
RHYTHM-ICD [104]	119	0	59	0	178
VECTOR [40]	0	59	0	47	106
Total	**171**	**117**	**211**	**213**	**712**

4.3.3 Follow-up

The longest available follow-up (primary endpoint analysis) was requested from all manufacturers in the data request form. Longer follow-up has the potential to provide more information regarding long-term baseline risk and treatment effects than the original trial publications[1].

[1] No long term follow-up was provided for CARE-HF though this has been published [57;105]. 8

Cross-over from the control to active arm may lead to improvements in outcomes in the control arm that would not be observed in a true parallel group design. A review of the rates of cross-over in the trials suggested that use of the longest follow-up may be susceptible to bias. Cross-over was observed to be particularly high in trial designs where the active arm device was implanted for all patients with control arm patients receiving none or only part of the device functionality ('on/off' design). In these trials, almost all patients in the control arm crossed over once patients were unblinded.

Table 33 shows the proportion of patients receiving an 'upgrade' during the trial follow-up provided. An upgrade was defined as a switch from OMT to an active device (ICD, CRT-P or CRT-D); a switch from ICD to CRT-D or a switch from CRT-P to CRT-D.

Table 33: Cross-over during follow-up provided for IPD Trials

Trial	On/Off design?	% Upgrade in control arm
CARE-HF	No	13% (OMT)
COMPANION	No	34% (OMT) 7% (CRT-P)
CONTAK_CD ph1	Yes	NA
CONTAK_CD ph2	Yes	NA
DEFINITE	No	12% (OMT)
MADIT	No	NA
MADIT-CRT	No	16% (ICD)
MADIT II	No	6% (OMT)
MIRACLE	Yes	91% (OMT)
MIRACLEICD	Yes	94% (ICD)
RAFT	No	11% (ICD)
RethinQ	Yes	NA
REVERSE CRT-D US	Yes	100% (ICD)
REVERSE CRT-D Eu	Yes	98% (ICD)
REVERSE CRT-P US	Yes	100% (OMT)
REVERSE CRT-P Eu	Yes	96% (OMT)
SCD-HeFT	No	11% (OMT)

Based on this information, only the protocol specified original 'data lock' follow-up

year follow-up of MADIT II has been published[102], however this was not supplied for this analysis as the follow-up data are not owned by Boston Scientific.

was included in the analysis, i.e. beyond the date or follow-up time periods specified for database-lock all patients are censored. This is expected to limit the amount of cross-over as within these periods blinding and/or protocol requirements limited the amount of cross-over observed.

The date or time period cut-offs used are provided as Table 34, along with the median follow-up times available once the database-lock cut-offs are applied. These ranged from 3 to 40 months across trials. For some trials, longer term follow-up has been reported in the literature, this information is summarised in section 3.9.

Table 34: Follow-up period used in analysis of IPD Trials dataset

Trial	Database lock	Median follow-up[a]	Availability of longer follow-up in literature
CARE-HF	Sept 30th 2004	25 months	Yes
COMPANION	Dec 1st 2002	16 months	No
CONTAK_CD ph1	3 months follow-up	3 months	Yes
CONTAK_CD ph2	6 months follow-up	6 months	No
DEFINITE	May 25th 2003	27 months	No
MADIT	March 24th 1996	24 months	No
MADIT-CRT	June 22nd 2009	29 months	No
MADIT II	Nov 20th 2001	18 months	Yes
MIRACLE	6 months follow-up	6 months	No
MIRACLEICD	6 months follow-up	6 months	No
RAFT	Not specified	39 months	No
RethinQ	6 months follow-up	6 months	No
REVERSE CRT-D US	12 months follow-up	12 months	No
REVERSE CRT-D Eu	24 months follow-up	24 months	No
REVERSE CRT-P US	12 months follow-up	12 months	No
REVERSE CRT-PEu	24 months follow-up	24 months	No
SCD-HeFT	Oct 31st 2003	41 months	No[b]

a) calculated from IPD, includes all patients with all patients still alive censored at database lock; **b)** 10 year follow-up of SCD-HeFT is expected to become available during the course of this appraisal.

As the dataset requested comprised the longest follow-up available for most trials, rather than the protocol specified analysis, a comparison of the deaths in each trial in the database (up to the database lock point) with the trial publications was conducted. Exact replication was possible for all trials with the exception of the MADIT trial (2 additional deaths in the ICD arm were thought to have occurred prior to database lock but have been reported afterwards) and

REVERSE (not possible to reconcile as data reported in publications[106] refers to two non-mutually exclusive populations).

4.3.4 Covariables considered

Previous NICE appraisals of the devices[35;36] have made recommendations for specific subgroups of patients. It is important that our analysis captures any covariables that are likely to be baseline risk modifiers or treatment effect modifiers in order to both address heterogeneity between trials and to aid accurate prediction of cost-effectiveness in subgroups.

However, it is important to note that inclusion of unimportant covariables increases both uncertainty in parameter estimates and the number of subgroups for which predictions are made[2]. For both of these reasons a parsimonious model is preferred.

Based on covariables used to define previous NICE recommendations, a review of existing risk scores, a review of treatment effect modifiers in previous RCTs and clinical opinion from two clinical specialists, the following covariables were identified as important for consideration in the analysis:

- Age
- Gender
- Country (US vs. non-US)
- New York Heart Association (NYHA) class
- Ischaemic aetiology
- Left ventricular ejection fraction (LVEF)
- QRS
- Left bundle branch block (LBBB)

Key variables not considered further, and the reasons for this, are provided below:

- History of MI – this is highly correlated with ischaemic aetiology. The clinical

[2] For example, inclusion of ischaemia (yes/no); NYHA (1/2/3/4); gender and an age covariable split in to five levels results in 80 subgroups (2 x 4 x 2 x 5).

experts consulted suggested that ischaemic aetiology may be a more reliable covariable as MIs may not be recorded in many cases. In addition, ischaemic aetiology was missing in fewer cases than history of MI (6.4% vs. 22.5%).

- History of atrial fibrillation (AF) – history of AF as opposed to current AF was not thought to be a useful differentiator. It was also thought to be potentially unreliable due to the dependence on the recording of AF in patients' medical notes.
- Sinus rhythm – this is potentially an important covariable, and is thought to modify CRT efficacy. However, of the ten CRT-P or CRT-D trials included in the IPD Trials data set, only the RAFT trial included a minority of patients with permanent atrial fibrillation[3]. Hence, almost all patients in these studies were in sinus rhythm (by virtue of the relationship: proportion in sinus rhythm = study population – proportion in AF)
- Mechanical dyssynchrony – these data were collected in a single study (CARE-HF) and could not therefore be considered in the analysis. In addition, this component of the CARE-HF inclusion criteria is unlikely to have driven the trial's results, as discussed in Section 4.5.4.
- Prior pacing – very few patients included in the IPD Trials had prior pacing. This was allowed in only two trials, RAFT and MADIT II (and possibly MADIT though this was never explicit). The number of patients with prior pacing in these trials is thought to be small, and patients with prior pacing could only be identified exactly in MADIT II. This covariable was therefore not included in the analysis.
- History of spontaneous VT/VF – although this was identified as a potentially important covariable, an initial review of the baseline data by the clinical experts suggested that the definitions used across trials were unlikely to be consistent and that the analysis should not therefore include this data.
- Non-sustained VT on ECG – this was not tested for in the majority of the studies (only MADIT and DEFINITE collected these data for all patients.

[3] MIRACLE ICD inclusion criteria stated "Chronic atrial arrhythmias, or cardioversion or paroxysmal atrial fibrillation within previous 1 month". This is assumed to exclude all patients with permanent atrial fibrillation at the time of enrolment.

- Inducible VT on electrophysiology testing – this was not tested in the majority of the studies (only MADIT required electrophysiology testing for all patients prior to enrolment).
- Diuretic use – although potentially an important proxy for disease severity in addition to NYHA and LVEF[107], this covariable was not included in the analysis as it is not expected that NICE would make a recommendation contingent upon something that was subject to frequent individual titration.

Descriptors of the included covariables are provided as Table 35. The most notable differences are that patients enrolled in CRT trials have on average a higher NYHA class, more prolonged QRS and are more likely to have LBBB (as the likelihood of LBBB increases with widened QRS) than in ICD trials.

Table 35: Covariable data for IPD Trials dataset

Device	OMT	CRT-D	CRT-P	ICD	Missing (%)
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QRS (mean, ms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LVEF (mean, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (% Female)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
US (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA1 (%)	[redacted]	[redacted]	[redacted]	[redacted]	
NYHA2 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA3 (%)	[redacted]	[redacted]	[redacted]	[redacted]	
NYHA4 (%)	[redacted]	[redacted]	[redacted]	[redacted]	
Ischaemic (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LBBB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The only covariable for which a significant proportion of data is missing is ischaemic aetiology, though the proportion of data missing is still relatively low ([redacted]).

Data from the most recent Cardiac Rhythm Management UK National Audit (2010)[21] was used to compare, where possible, the above covariable pattern with that observed in UK clinical practice. The key statistics are reproduced in Table 36.

Table 36: UK Summary data (reproduced from Cunningham et al., 2010)

Device	CRT-D	CRT-P	ICD
Age (mean, years)	67.1	71.7	63.1
QRS (prolonged, %)	77.6%	84.3%	32.1%
LVEF (mean, %)	N/A[1]	N/A[1]	N/A[1]
Gender (% Female)	16.6%	31.6%	19.9%
NYHA class I (%)	11%	2%	44%
NYHA class II (%)	18%	10%	38%
NYHA class III (%)	64%	85%	16%
NYHA class IV (%)	7%	3%	1%
Ischaemic (%)	64.5%	33.1%	66.3%
LBBB (%)	N/A	N/A	N/A

1) data reported as “Good”, “Fair” or “Poor” with no numerical quantification of each category provided

Note, that a number of these parameters, in particular the percentage in each NYHA class, have been distorted by previous NICE decisions (for example, CRT not being formally approved for use in NYHA class I/II etc.). Similarly, other data are presented in differing formats to that in the trial database (e.g. QRS reported as normal/ prolonged). There was also a high level of missing data in the UK National Audit data. Hence, direct comparison of the UK database with the trial database not always possible. Nonetheless, where a fair comparison is possible, the trial database is broadly reflective of the UK population.

4.3.5 Handling of continuous covariables

The continuous covariables (age, LVEF and QRS duration) were converted to categorical equivalents, both to ensure that the analyses provide clear recommendations for clinicians and to avoid technical issues with the cost-effectiveness model[4]. A description of the cut-offs used for each variable and the rationale for these is provided below.

- Age – age was split in to the following categories: 0-≤55, >55-≤65, >65-≤70, >70-≤75, >75. This provided a reasonable compromise between ensuring that there were sufficient patients in each category and capturing the difference in

[4] Due to the non-linear relationship between covariables in a survival analysis and mean life years gained, inclusion of continuous covariables would necessitate simulating a large number of patients through the cost-effectiveness modelling. Using dichotomous covariables allowed use of a more parsimonious approach with fewer simulations.

prognosis and potentially treatment effects across categories.

- LVEF - Previous NICE recommendations have used cut-offs of 35% and 30%. The following categories were used to ensure an even spread across categories and to capture clinically meaningful differences in prognosis: 0%-≤20%, >20%-≤25%, >25%-≤30%, and >30%. It should be noted that only a small number of patients in the database [redacted] had an LVEF>35%. The >30% category is therefore representative of patients with LVEF >30%-≤35%, however to avoid excluding data the patients with LVEF>35% are retained in this category.
- QRS - Previous NICE recommendations have used cut-offs of 120ms and 150ms. The following categories were therefore used in the analysis: 0-<120ms, ≥120ms-<150ms, and ≥150ms.

4.3.6 Missing data

Data regarding study, treatment allocation, and time to death or loss to follow-up was complete for all trials. As documented in Section 4.3.3, for the covariables included in the analysis there were some missing data [redacted] depending on the covariable). To enable an intention to treat analysis, covariable values for these data points were imputed using multiple imputations. Details of the imputation approach are provided in Appendix six.

Multiple imputation was used for all analyses other than the exploratory analyses, which were based on complete cases only. To avoid exclusion of a substantial number of patients from the exploratory analysis, missing values of the Ischemia variable were imputed directly from the MI variable (exploratory analyses only). Use of a complete case analysis for exploratory purposes (including covariable selection) is likely to be robust for this data set as [redacted] of patients had complete data.

4.4 Description of analyses

4.4.1 Baseline

In order to generate estimates of baseline mortality risk, parametric survival analyses were run on a pooled data set including all patients randomised to OMT. OMT was chosen as the baseline as this allowed for inclusion of a heterogeneous

population of patients (and importantly, patients randomised to an ICD alone and a CRT-P alone).

The baseline analysis was independent of the treatment effect analysis. Although it would be possible to simultaneously analyse the baseline and treatment effects this would require a constrained functional form for the baseline hazard. Use of an unconstrained baseline has been generally preferred in meta-analysis and network meta-analysis.

The following parametric survival distributions were run for the all-cause mortality endpoint: exponential, Gompertz, log-logistic, log-normal, and Weibull. Favoured distributions were trialled with and without covariables. Initial analyses suggested that for patients with a milder prognosis, the models gave unrealistic long term predictions, with a greater proportion of patients predicted to be alive than would be expected in the general population.

An alternative approach was therefore applied whereby age was included as a time-dependent covariable. The advantage of this approach is that information is borrowed across patients in two ways:

1) The model parameters take account of the fact that patients who are aged 65 at five years post baseline are expected to experience a similar modification to the risk of death (controlling for other prognostic variables) as patients who are aged 65 years at baseline;

2) The extrapolation process uses information on the inflated risk of death associated with being in the higher age categories to inform the increase in risk of death experienced as patients progress through the model.

This approach required inclusion of separate observations for each covariate value for each patient. As age changes continuously this would have required an infinite number of observations. To maintain reasonable run times for the analysis, updating of age as a time-dependent covariable was therefore conducted every 30 days.

The different parametric models excluding covariables were compared using the following metrics, in order to identify models found to be clearly inferior:

- Visual comparison of the fitted and Kaplan Meier survival curves for fit within trial follow-up

- Visual review of the extrapolation
- Visual review of the shape of the instantaneous hazard over time
- Comparison of Akaike's Information Criteria (AIC[108])
- Inspection of Cox-Snell residuals[108]

Any models found to be clearly inferior based on these tests were excluded from further consideration. All other models were trialled with the covariable set. This was conducted using a stepwise procedure based on AIC (forward and backward selection, two degrees of freedom for the penalty). The parametric models including covariables were then compared using the following metrics:

- AIC
- Cox-Snell residuals
- Tests for the acceptability of the proportional hazards assumption (exponential; gamma; Gompertz; Weibull) or accelerated failure time assumption (log-logistic; log-normal) with respect to each covariable were run
- Comparison of the fitted and Kaplan Meier curves for each quartile of the risk score (linear predictor component of the model) as recommended in Collett 2003[108]

Results of the final model were reviewed by clinical experts for plausibility. Long term (extrapolated) predictions of the final model were reviewed against available external data and with clinical experts to ensure their plausibility.

4.4.2 Network meta-analysis – overview

The aim of the network meta-analysis was to estimate relative treatment effects comparing each device to the other devices and OMT. Network meta-analysis (also described as mixed treatment comparison) enables the combination of trials that compare different sets of treatments, and form a network of evidence, within a single coherent analysis[109], and to use all available direct and indirect evidence to inform a given comparison between treatments. This is important for the current appraisal where some comparisons have little direct data but a large volume of indirect data, for example only patients randomised to OMT and CRT-D in COMPANION provide direct data comparing these treatments, whereas all other trials in the network provide indirect data informing this comparison.

Network meta-analysis is based on the assumption that, on a suitable scale, we can add and subtract within-trial estimates of relative treatment effects, i.e. the difference in effect between treatments A & B (d_{AB}) is equal to the difference in effects between treatments A & C and B & C ($d_{AB} = d_{AC} - d_{BC}$)[109-111] on a chosen scale.

Due to data availability, network meta-analyses are typically based on published aggregate data (typically from whole trials, but also from published subgroup analyses). In this context, opportunities to adjust for differences across trials which may be acting as treatment-effect modifiers are limited by data availability. The main approaches used are meta-regression and analyses of subgroup data.

As outlined in Section 4.3.2 for this submission, patient level data were made available for a large proportion of patients included in the network of evidence. This provided a unique opportunity to adjust for differences across trials in patient characteristics which may be acting as treatment-effect modifiers. This has the advantage of allowing subgroup-specific treatment effects to be estimated and potentially allowing heterogeneity or inconsistency in the network to be addressed.

4.4.3 Network meta-analysis – covariables excluded

The first analyses conducted took a more traditional form and analysed data aggregated by trial. The objective of these analyses was to understand the efficacy estimates produced by synthesising the overall evidence base without

adjustment; the extent of agreement between network meta-analysis, pairwise meta-analysis and individual trial estimates of treatment effect; and the impact of restricting the All Trials dataset to the IPD trials only.

The methods and code used in the network meta-analysis have been described previously; analyses were run using R to WinBUGS[112]. These analyses were run without covariables. Hazard ratios were used for all IPD Trials, as these trials all reported dates of randomisation and dates of death or last follow-up for mortality.

For the non-IPD trials no hazard ratio data were reported in the trial publications, binary data were therefore included for these trials. Given the two datasets and the possibility of both fixed and random effect analyses the following four analyses were run:

1. All Trials, Fixed effects
2. All Trials, Random effects
3. IPD Trials, Fixed effects
4. IPD Trials, Random effects

Two sets of initial values were used and convergence was assessed by examining caterpillar plots and Brooks Gelman-Rubin (BGR) statistics. Autocorrelation was also examined. The deviance information criteria (DIC) was used to compare the fit of the fixed and random effects models.[113] The number of burn in simulations and model runs was determined based on inspection of these statistics for each model.

4.4.4 Network meta-analysis – Covariables included

A second set of analyses were run incorporating the covariable set as potential treatment effect modifiers. These analyses used data from the IPD Trials only and used fixed effects analyses only. A discussion of why the analysis was restricted to a fixed effects analysis is presented in appendix seven.

The network meta-analysis was run using individual patient data (IPD) analysed using a frequentist Cox proportional hazards analysis, stratified by study. The regressions included main effects for the devices; main effects for the covariables (nuisance parameters) and interactions between the devices and covariables. This method generates equivalent results to a fixed effects Bayesian network

meta-analysis using non-informative priors. The methods generate equivalent results because stratifying by trial allows the baseline hazard in each study to be independent. This method has previously been used by Tudor Smith *et al*.[114;115] in a network meta-analysis of epilepsy trials. Covariables were selected for inclusion based on univariate analyses, a multivariate stepwise procedure and review of these exploratory analyses with the clinical experts. Proportional hazards tests were then run on the preferred model for all main effects and interaction effects. The Schoenfeld residual-based test suggested by Grambsch and Therneau was used.[116]

Further detail regarding the model used and the approach for covariable selection is provided as Appendix eight.

4.5 Results

4.5.1 Baseline risk

Firstly, parametric models were fitted without covariables. All curves exhibited a good fit and produced similar predictions within the trial period. Beyond this the exponential, Weibull and Gompertz distributions all made similar and reasonable predictions (although predicted slightly long 'tails'). The log-normal and log-logistic distributions produced unrealistic extrapolations with approximately a fifth of the patients being alive when the average age of the patients in the cohort reached 100 years.

The AICs supported use of the exponential (AIC: 16,329), Weibull (16,329) or log-logistic (16,329) over the Gompertz (16,332) or log-normal (16,358).

Plots of the Cox-Snell residuals suggested that the models without covariables all provided a similar fit with the exception of the log-normal model which provided a poorer fit.

Examination of the instantaneous hazard indicated that it was reasonably constant over time. The exponential and Weibull distributions were therefore considered for the final model.

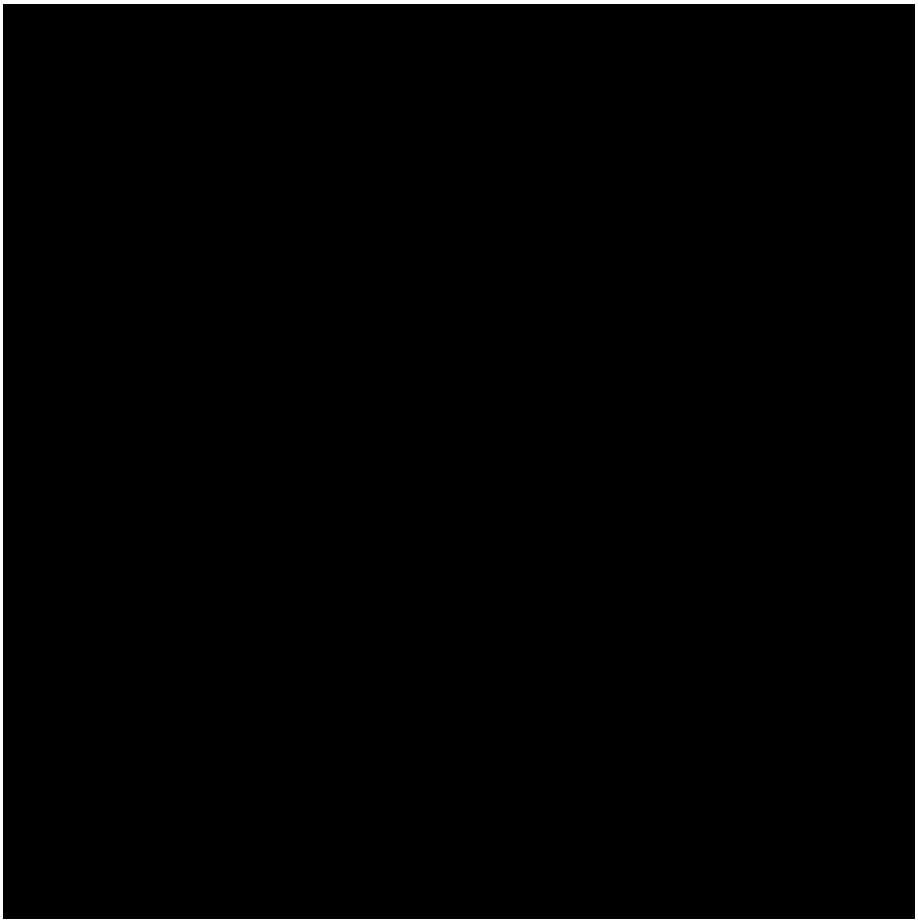
All covariables trialled were retained by the stepwise procedure and found to be highly significant predictors of baseline risk, with the exception of the US and LBBB variables. Inclusion of the covariables suggested the following conclusions (which held across the exponential and Weibull distributions):

- Age, Gender, Ischemic aetiology, and LVEF all exhibited trends in the direction and of the magnitude expected. The log hazard ratio for age indicated a linear relationship with mortality.
- NYHA classes III/IV patients as expected performed worse compared to NYHA classes I/II patients (NYHA class IV was the characteristic with the largest effect on risk of death, as expected). Patients in NYHA class II exhibited an almost identical risk of mortality compared to those in NYHA class I; these categories were therefore collapsed.
- QRS duration <120ms was associated with improved outcomes compared to QRS duration ≥150ms. Patients with QRS duration of ≥120ms-<150ms exhibited an almost identical risk of mortality compared to those with QRS duration ≥150ms. For exploratory purposes an analysis including only QRS as a continuous variable, with a quadratic form, was therefore run. This showed deterioration in mortality as QRS increased up to about 120-130ms and then a flattening out beyond this point. It was therefore judged reasonable to pool the ≥120ms-<150ms and ≥150ms categories for the purposes of the baseline risk analysis.

Both plots of the Cox-Snell residuals and the AIC statistics (15,597 for exponential model and 15,594 for Weibull model) suggested a better fit for the Weibull model.

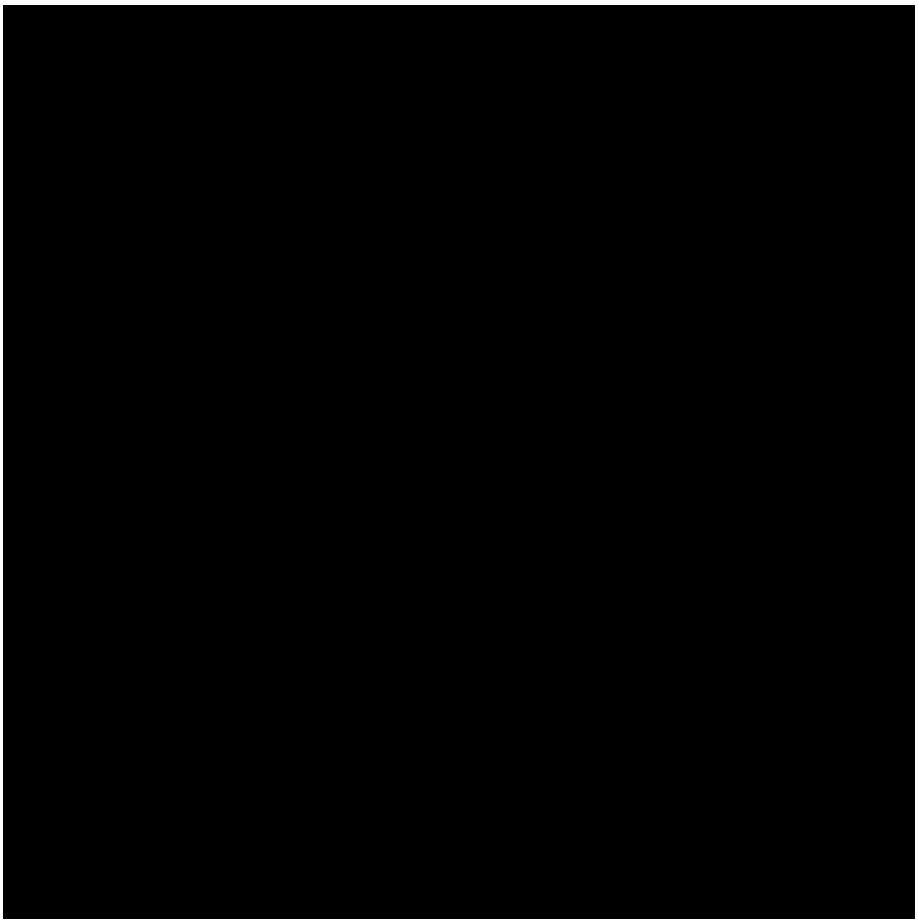
Comparisons of the Kaplan Meier curves for patients in each quintile of the risk distribution suggest that this Weibull model is able to differentiate between patients with quite different risk profiles (see Figure 13). This presentation also shows the heterogeneity in the patient population analysed, with only [redacted] of patients in the quintile with the lowest predicted survival surviving at 4 years, compared to [redacted] of those in the quintile with the highest predicted survival.

Figure 13: Comparison of Kaplan Meier and parametric curves for patients in different risk quintiles (risk quintiles defined by the parametric model)



A Cox proportional hazards version of the preferred model was run in order to assess the suitability of the proportional hazard assumption. This suggested that one variable, age, was not conforming to the proportional hazards assumption. This is not entirely surprising as it would be expected that the increase in mortality risk for older patients would increase more rapidly over time than observed for younger patients. In addition, inspection of the predictions for a longer time horizon (see Figure 14) suggested that the model was over predicting survival in low risk patients.

Figure 14: Predictions over 50 year time horizon (by risk quintiles)



To address these issues, age was incorporated as a time-varying covariate in the analysis. Inclusion of baseline age assumes that baseline age modifies the hazard of death in a proportionate manner throughout the model. Inclusion of age as a time-varying covariate instead assumes that the impact of being at a specific age at a particular time point modifies the hazard of death in a proportionate manner.

With the application of this approach it was also considered appropriate to include age as a continuous covariable in order to allow the increase in the hazard of death associated with ageing to be applied continuously in the model. This was also thought valid as inspection of the coefficients on the age variable suggested a linear increase in the log hazard ratio over the age range in the database.

The preferred model is summarised as Table 37. This is the model for baseline mortality used in the cost-effectiveness model. For the purposes of the cost-effectiveness modelling these parameters can be converted to a survival curve using the following formulae:

$$h(t) = \exp(-(\log(scale) - \boldsymbol{\beta} \cdot \boldsymbol{X}) \cdot shape) \cdot shape \cdot t^{shape}$$

$$S(t) = \exp(-\int_0^t h(t)\,dt)$$

where h(t) is the instantaneous hazard, S(t) is the survival curve, **β** are the coefficients on the covariables and the **X** are the set of covariables (which can be time-dependent).

Table 37: Preferred baseline risk model

Variable	Coefficient	Hazard ratio for prognostic variable[a]	P-value
Age (per year)	[redacted]	[redacted]	[redacted]
Male gender	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	[redacted]	[redacted]	[redacted]
QRS duration <120ms	[redacted]	[redacted]	[redacted]
LVEF>20% and <=25%	[redacted]	[redacted]	[redacted]
LVEF>25% and <=30%	[redacted]	[redacted]	[redacted]
LVEF>30%	[redacted]	[redacted]	[redacted]
log(scale)	[redacted]	[redacted]	[redacted]
log(shape)	[redacted]	[redacted]	[redacted]

(a) Hazard ratio = exp(β/shape); Na = not applicable

The impact of including age as a time-dependent covariable relative to including baseline age only, and relative to general population mortality, is shown as Figure 15 (patient shown has the average characteristics of patients in the lowest risk quintile). This shows the similar predictions associated with the models within the period of trial follow-up, and the more plausible long term predictions associated with the model that includes age as a time-dependent covariable.

An example curve for the average patient in the highest risk quintile is shown as Figure 16 to illustrate the minimal impact of the analytical approach on high risk cohorts, where a much larger proportion of events occur within the available

follow-up.

Predictions for sample patients were reviewed with clinicians, who supported their plausibility.

Figure 15: Example predictions, with and without age as time-dependent covariable: low risk patient (male, age 51 in NYHA class I/II, non-Ischaemic aetiology, QRS duration <120ms and LVEF between 25% and 30%)

Figure 16: Example predictions, with and without age as time-dependent covariable: high risk patient (male, age 71 in NYHA class III, ischaemic aetiology, QRS duration>120ms and LVEF ≤20%)

4.5.2 Network meta-analysis – no covariables

Figure 17 presents the results for each of the four models fitted for each pairwise comparison for which direct data is available[5]. This shows that the mean estimates from the fixed and random effects analyses for each data set are broadly similar, though confidence intervals associated with the random effects analysis are wider. The DIC assessment of model fit supported use of the fixed effect (FE) as opposed to random effect (RE) model for the All Trials (FE DIC = 59.0 vs. RE DIC = 60.8) and IPD Trials (FE DIC = 1.4 vs. RE DIC = 3.0) analyses.

Results for All Trials and IPD Trials show little difference; this is unsurprising given the small proportion of patients for whom IPD were not available (5%) but is reassuring given the reliance of subsequent analyses (including the final model that informs the cost-effectiveness analysis) on the IPD Trials.

All devices when compared to OMT deliver a statistically significant benefit (at P=0.05) across analyses. The magnitude of effect is also notable with hazard ratios vs. OMT (mean (95% credible interval, CrI)) of [redacted] for CRT-D; [redacted] for CRT-P and [redacted] for ICD (fixed effects analysis of All Trials).

[5] Fixed effects models were run for 20,000 burn-in simulations and a further 50,000 iterations, random effects models were run for 100,000 burn-in simulations and a further 200,000 iterations (with thinning rate = 5).

Figure 17: Comparison of network meta-analysis results using IPD Trials and All Trials, and fixed and random effects models

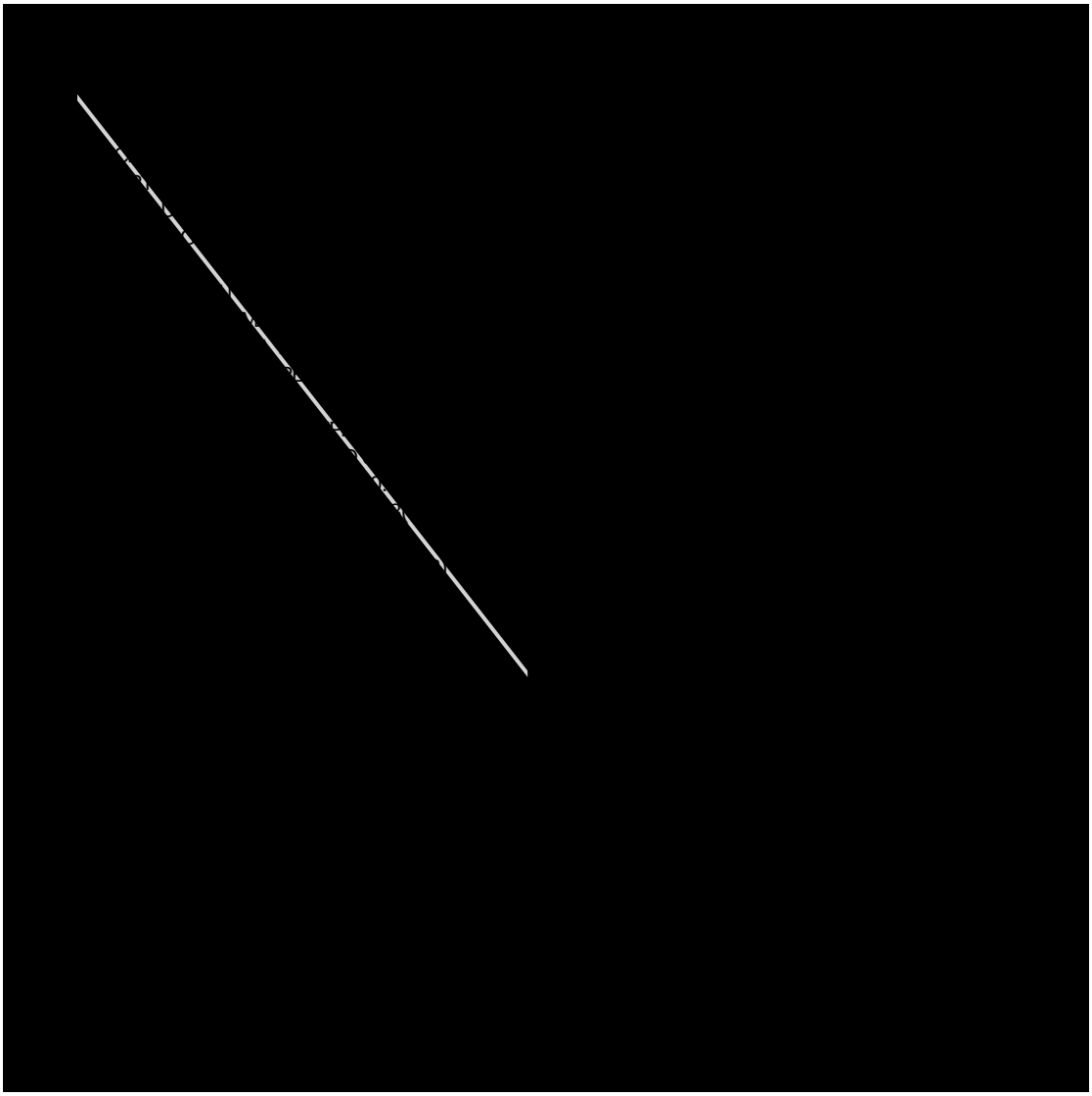
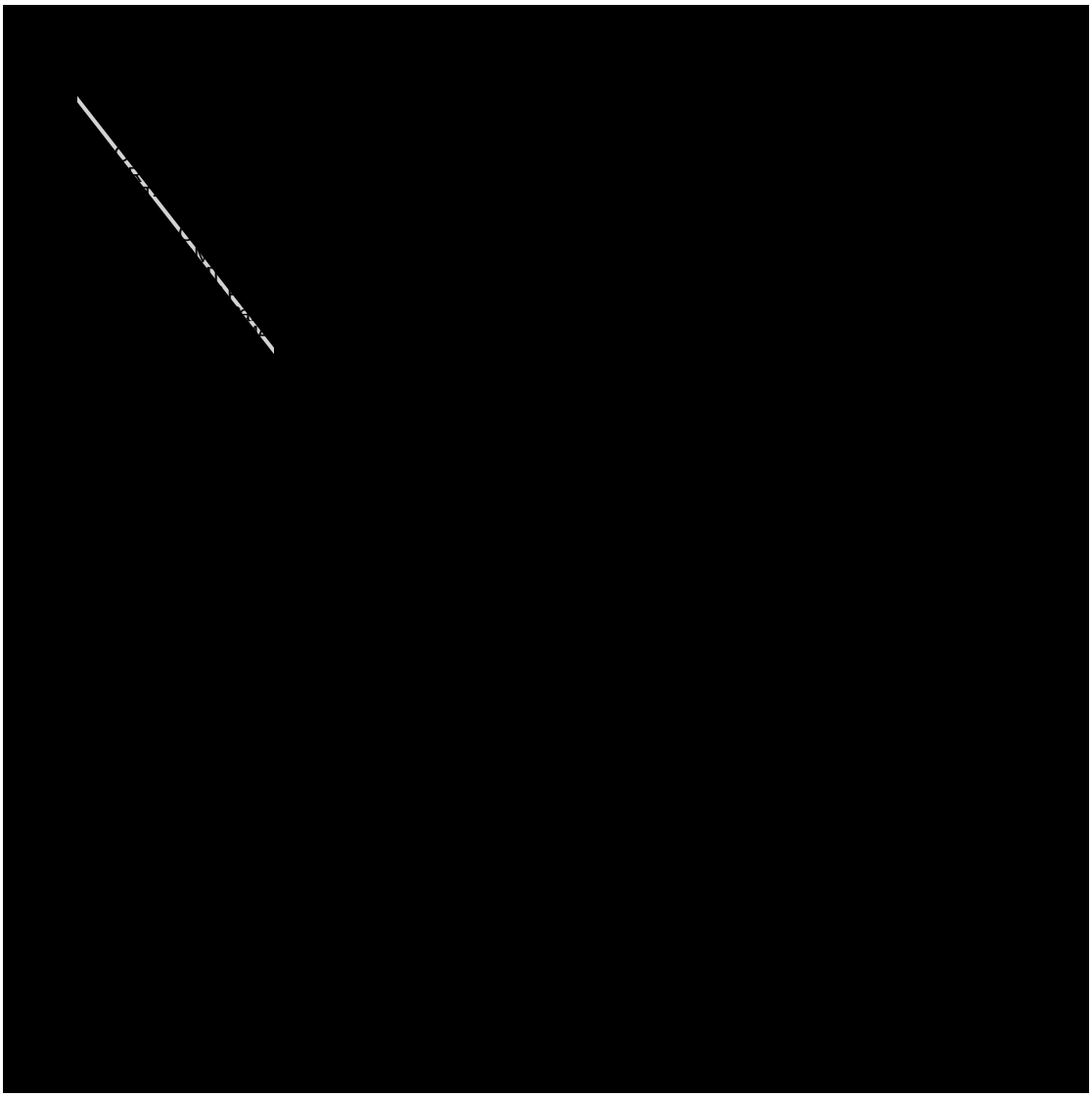


Figure 18 compares the FE results for IPD Trials (the focus of our analysis of heterogeneity) with the individual trial results and pairwise meta-analyses of the direct data for each comparison. The network appears to be reasonably consistent. Good concordance between the pairwise meta-analysis and network meta-analysis results suggests reasonable concordance between the indirect and direct data.

There is some heterogeneity within pairwise comparisons. The CARE-HF trial outperforms the other trials comparing CRT-P to OMT. This may be due to the inclusion criteria of CARE-HF, which required patients to have QRS≥120ms and mechanical dyssynchrony OR QRS≥150ms. This inclusion criterion appears to

have resulted in almost all patients with QRS<150ms being excluded (these patients comprise only [redacted] of the cohort compared to [redacted] in the Companion cohort; [redacted] in the MIRACLE cohort and [redacted] in the REVERSE CRT-P cohort). The MADIT trial also appears to be an outlier, exhibiting much stronger effects than the other ICD vs. OMT trials. This may be due to the higher proportion of males in this trial or the requirement for prior MI (though this also applies in MADIT II), or that this simply a smaller trial than the others comparing these treatments. It may also be because background drug therapy was not as good as in subsequent trials.

Figure 18: Comparison of Fixed Effects IPD Trials analysis to individual trial results



4.5.3 Treatment effects over time

An important question is the extent to which treatment effects of the devices are

maintained over time. Tests of the proportional hazards assumption suggested no violation of this assumption (global p-value for device terms = [redacted]), nor did plots of the Schoenfeld residuals suggest time trends.

4.5.4 Network meta-analysis – covariable selection

The results of the univariate analyses and multivariate stepwise selection procedures are summarized in Appendix eight. Appendix nine presents the univariate analyses graphically.

The exploratory analyses were reviewed with two clinical experts and the following conclusions were reached regarding the final model:

- Clinical covariables:
  - *NYHA* – the univariate analysis suggests a somewhat diminished effect of CRT-D in patients in NYHA class IV. NYHA class was retained in only one of the multivariate models, as a treatment effect modifier for CRT-D. This result is driven by the poorer efficacy of CRT-D in NYHA class IV patients. The low statistical significance for this factor in the univariate analysis and omission from the other multivariate models may be attributable to the nine degrees of freedom lost when modelling the NYHA-device interaction. A NYHA class 4-device interaction is therefore included in a sensitivity analysis, given the plausibility of a diminished effect of CRT-D in this patient group, where the ratio of heart failure to sudden cardiac deaths becomes much higher, and therefore the benefit of the ICD component of the device is likely to be diminished.
  - *Ischaemic aetiology* – the univariate and multivariate analyses did not suggest that ischaemic aetiology impacts on the relative effects of the devices. This variable was therefore excluded from the final model.
  - *LVEF* – no clear trend with respect to LVEF was observed across the analyses. The analyses suggest a trend for increased efficacy of CRT-D in patients with lower LVEF. For CRT-P and ICD, a peak in efficacy is observed around a LVEF of 30%. This is counter intuitive (as CRT-D combines the therapies delivered by CRT-P and ICD) and suggests that the relationship between LVEF and CRT-D efficacy may have

occurred by chance. This finding was therefore not considered sufficiently robust to be included in the model.

- *QRS* – QRS duration acted in the expected direction in the multivariate and univariate analyses with patients with QRS duration ≥150ms experiencing better CRT-P and CRT-D efficacy than patients with QRS duration ≥120 to <150ms. For ICD, patients with QRS duration ≥120ms to <150ms experienced better efficacy than those with shorter and longer QRS duration. Evidence of an interaction effect was shown in all analyses where QRS duration was considered as a continuous covariable. QRS duration was therefore included in the final model.
- *LBBB* – LBBB acted in the expected direction in the multivariate and univariate analyses with patients with LBBB experiencing higher efficacy of CRT-P and CRT-D than patients with non-LBBB conduction abnormalities (right bundle branch block or non-specific intraventricular conduction delay). LBBB was therefore included in the final model.

  It should be noted that the high level of collinearity between LBBB and QRS duration may explain why both covariables are not retained in all stepwise analyses.

- Non-clinical covariables:
  - *US vs. non-US* – US was retained as a covariable in three of the multivariate analyses, though it was not statistically significant in the univariate analysis. This result is likely to be in part by driven by the European RAFT trial comparing CRT-D to ICD, which provides the strongest evidence for this pairwise comparison. However, US terms were retained even once the RAFT trial was excluded. One possible hypothesis is that non-US patients tend to have a lower body mass index (BMI), which is associated with a higher risk of SCD[117]. However, due to limited collection of height data (missing in [redacted] of patients) this could not be explored robustly using the current data set. It therefore seemed safest to exclude the US term as it may be capturing systematic differences between trials conducted in US and

ex-US geographies, and its inclusion would have biased the results in favour of device therapy.

- *Age* – age acted in the expected direction in the multivariate and univariate analyses, with younger patients experiencing stronger ICD efficacy and older patient's stronger CRT efficacy. This is likely to be attributable to younger patients being relatively more likely to die from sudden cardiac death. Age was statistically significant when included as a continuous covariable in the univariate analysis, and was retained in all multivariate analyses. Age is therefore included in the final model.
- *Gender* – gender acted in the expected direction in the multivariate and univariate analyses with male patients experiencing stronger ICD efficacy and female patients stronger CRT efficacy. Again, this is likely to be attributable to males experiencing a higher likelihood of sudden cardiac death. Gender was statistically significant in the univariate analysis and retained in all multivariate analyses. Gender is therefore included in the final model.

In summary: QRS duration, LBBB, Age and Gender are included in the model as device treatment effect modifiers. A dummy variable for being in NYHA class 4 is added in a sensitivity analysis. As QRS duration and Age are continuous covariables, the dichotomisations chosen for the exploratory analyses were re-examined for their appropriateness. A quadratic model was fitted for both covariables. This showed that for QRS the efficacy of CRT-P and CRT-D increases broadly linearly between QRS durations of 120ms and 150ms and then levels off at 150ms. This suggests that the current dichotomisation is reasonable, though may miss some of the heterogeneity in response to therapy in the 120-150ms category. For age, efficacy of ICD increases and of CRT-P decreases with age, until a plateau is observed after approximately 60 years. For simplicity, age was therefore converted to a two level variable of <60 and ≥60 years. Again this may miss some of the heterogeneity in response to therapy in the <60 category.

Given the uncertainty regarding the magnitude of the treatment effect modifiers it was decided that covariables should be allowed to modify all device treatment effects in the final model.

Table 38: Results of univariate analysis and multivariate automated stepwise analyses used to inform interaction effect selection

Covariable	Univariate analysis p-value[a]		Retention following multivariate automated stepwise procedure[b]			
			Device specific modifiers		All-device modifiers	
	Continuous variables dichotomised	Continuous variables retained	Continuous variables dichotomised	Continuous variables retained	Continuous variables dichotomised	Continuous variables retained
Age	■	■	■	■	■	■
Gender	■		■	■	■	■
Country (US vs. ex-US)	■		■	■		■
NYHA	■			■		
Ischemic aetiology	■					
LVEF	■	■		■		■
QRS	■	■		■		■
LBBB	■	■	■	■	■	

a - p-value for comparison of two times the difference in the log-likelihood for the model containing Device and Covariable main effects but no interaction, and the model containing Device and Covariable main effects and the Device*Covariable interaction (Chi-square test used). **b** - For the multivariate exploratory analysis, patients randomised in to CRT-D or CRT-P trials with QRS<120ms were excluded as the very low number of deaths (five in total in patients randomised to CRT-P and CRT-D) made any modelling of these patients unstable. This decision was replicated in the final analyses. This results in ■ patients being excluded from RethinQ; ■ from CONTAK-CD; ■ from CARE-HF; ■ from RAFT and ■ from MADIT-CRT. * p-value<0.05. ** p-value<0.01

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4.5.5 Network meta-analysis – preferred model

The preferred model is presented in Table 39, which shows the model parameters used in the cost-effectiveness model, and Figure 19 which show the predicted treatment effect for each subgroup, along with the associated confidence intervals. It should be noted that the analysis including treatment effect modifiers presented in this section is inherently more uncertain than the analysis without covariables presented in section 4.5.2. This is due to the increased number of parameters required to capture heterogeneity in treatment effects across patients with different characteristics. This illustrates the compromise between increasing the precision of the point estimates for specific subgroups, and minimizing the uncertainty in the treatment effects.

In general, caution should be taken not to over-interpret individual subgroups since anomalies may arise as a result of patient level characteristics not accounted for. Of further note is that the conclusions refer to the effect of treatment above and beyond the baseline risk observed for a given clinical covariate pattern (see Table 37). Nonetheless, the following broad conclusions can be drawn from these figures:

- **QRS duration <120ms**
  - Benefit of ICD apparent in males of any age
  - In females, the benefit of ICD appears to be restricted to patients aged <60 years
- **QRS duration ≥120ms to <150ms without LBBB**
  - CRT-D offers an advantage over CRT-P regardless of gender or age.
  - ICD may offer a similar benefit to CRT-D in males, with CRT-D the preferred option in females.
  - In males CRT-P may offer minimal benefit. The benefit in women of all ages is far more pronounced
- **QRS duration ≥150ms without LBBB**
  - CRT-D offers an advantage over CRT-P regardless of age of gender
  - ICD may offer a similar benefit to CRT-D in males <60 years, with

CRT-D preferred to ICD in all other groups.

  - In males <60 years CRT-P may offer minimal benefit and in females ≥60 years ICD may offer limited benefit. As with the results for QRS duration between 120 and 149ms, the benefits of CRT-P in all other patient groups are more pronounced.

- **QRS duration ≥120ms-<150ms or QRS duration ≥150ms with LBBB**
  - CRT-D offers an advantage over CRT-P regardless of age or gender.
  - While ICD and CRT-D both offer similar and substantive benefit in males <60 years, the benefits associated with CRT-D are slightly greater
  - In general, CRT-D offers greater benefit than ICD in females (compared to males) of all ages regardless of QRS duration
  - In females ≥60 years ICD may offer limited benefit.
  - In males <60 years CRT-P offers modest benefit if QRS duration is ≥120ms-<150ms and far greater benefit if QRS duration is 150ms or more.

The parameters used in the sensitivity analysis including NYHA class IV as a treatment effect modifier are presented in Appendix ten.

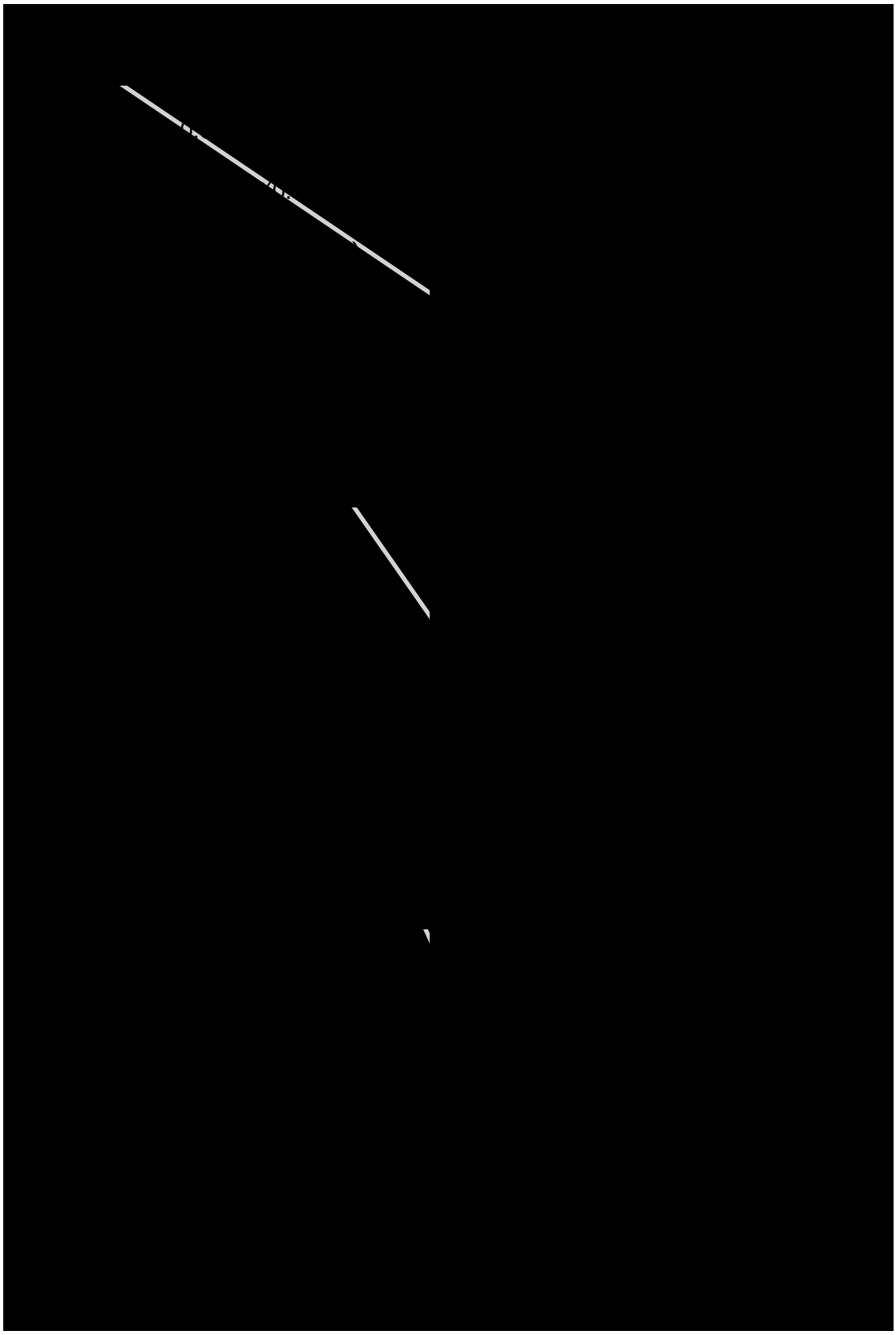
Table 39: Preferred model for IPD network meta-analysis

Variable[a]	Hazard ratio	P-value
ICD	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]
QRS<120	[redacted]	[redacted]
QRS>=120	[redacted]	[redacted]
LBBB	[redacted]	[redacted]
AGE>=60	[redacted]	[redacted]
GENDER=M	[redacted]	[redacted]
ICD*QRS<120	[redacted]	[redacted]
ICD*QRS>=120	[redacted]	[redacted]
ICD*LBBB	[redacted]	[redacted]
ICD*GENDER=M	[redacted]	[redacted]
ICD*AGE>=60	[redacted]	[redacted]
CRTP*QRS>=120	[redacted]	[redacted]
CRTP*LBBB	[redacted]	[redacted]
CRTP*GENDER=M	[redacted]	[redacted]
CRTP*AGE>=60	[redacted]	[redacted]
CRTD*QRS>=120	[redacted]	[redacted]
CRTD*LBBB	[redacted]	[redacted]
CRTD*GENDER=M	[redacted]	[redacted]
CRTD*AGE>=60	[redacted]	[redacted]

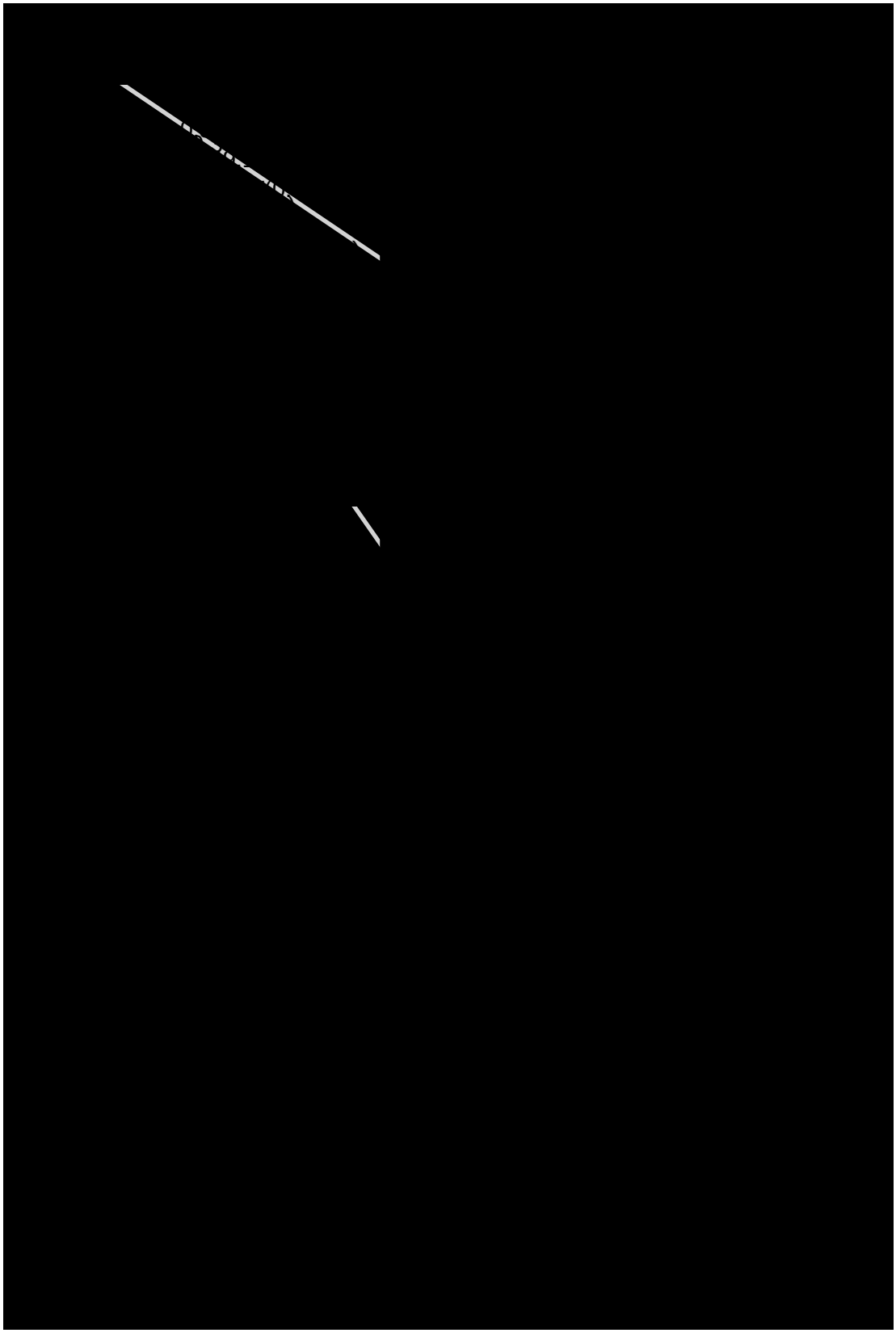
a – Reference category is a patient receiving OMT, <60 years of age, female, QRS duration ≥150ms and non-LBBB conduction abnormality. NB: main effects for covariables greyed out as not included in cost-effectiveness model.

Figure 19: Forest plot of results of analysis adjusting for covariables (LBBB)

(a) Non LBBB patients



(b) LBBB patients



4.6 Discussion of results

4.6.1 Baseline

The analysis of mortality risk for all patients randomised to OMT in the database (3,477 patients, followed up for up to up to 6.1 years) found NYHA class, ischaemia, QRS duration and LVEF all to be highly significant predictors of survival times, along with patient age and gender.

The risk equation developed was able to differentiate between the highly heterogeneous prognoses of patients included in the trials. For patients predicted to be in the upper 20% with respect to survival time, four year survival was [redacted] For patients predicted to be in the lowest 20%, four year survival was [redacted]

Inclusion of age as a time-dependent covariable in the analysis appeared to produce realistic predictions of survival both within the database follow-up period and when extrapolated over patient lifetime.

4.6.2 Network meta-analysis

A network meta-analysis was conducted including data from all studies identified by the systematic review – contingent on availability (12,638 patients followed up for up to 7.5 years).

- The analysis found CRT-D to have the strongest effect on all-cause mortality with a hazard ratio of [redacted] for CRT-D vs. OMT.
- Treatment effects for the individual devices were [redacted] for CRT-P vs. OMT and [redacted] for ICD vs. OMT (fixed effects analysis of All Trials).
- These results are similar to those published previously[118], and support the strong effect of all devices on the all-cause mortality endpoint.

Given the high level of heterogeneity in the patient groups under consideration, a series of analyses were conducted exploring the impact of patient characteristics on the magnitude of benefit associated with the devices. These analyses identified patients' age, gender and QRS morphology (both QRS duration and LBBB pattern) to be independently predictive of the magnitude of benefit associated with the devices. Younger patients and male patients appear more likely to benefit from ICD; the opposite is true for CRT. This is likely to be due to

the relatively higher rate of sudden cardiac death relative to other causes in younger and male patients[119;120]. The impact of QRS duration and LBBB is attributable to the CRT mechanism. The evidence for NYHA class IV as an effect modifier is equivocal but does suggest poorer efficacy of CRT-D in NYHA 4 patients.

A summary of the key findings is presented below. These conclusions all refer to patients with LVEF<35% and all NYHA classes:

- **QRS duration <120ms**
  - Benefit of ICD apparent in males of any age
  - In females, the benefit of ICD appears to be restricted to patients aged <60 years
- **QRS duration ≥120ms to <150ms without LBBB**
  - CRT-D offers an advantage over CRT-P regardless of gender or age.
  - ICD may offer a similar benefit to CRT-D in males, with CRT-D the preferred option in females.
  - In males CRT-P may offer minimal benefit. The benefit in women of all ages is far more pronounced
- **QRS duration ≥150ms without LBBB**
  - CRT-D offers an advantage over CRT-P regardless of age of gender
  - ICD may offer a similar benefit to CRT-D in males <60 years, with CRT-D preferred to ICD in all other groups.
  - In males <60 years CRT-P may offer minimal benefit and in females ≥60 years ICD may offer limited benefit. As with the results for QRS duration between 120 and 149ms, the benefits of CRT-P in all other patient groups are more pronounced.
- **QRS duration ≥120ms-<150ms or QRS duration ≥150ms with LBBB**
  - CRT-D offers an advantage over CRT-P regardless of age or gender.
  - While ICD and CRT-D both offer similar and substantive benefit in males <60 years, the benefits associated with CRT-D are slightly greater

- In females ≥60 years ICD may offer limited benefit.
- In males <60 years CRT-P offers modest benefit if QRS duration is ≥120ms-<150ms and far greater benefit is GRS duration is 150ms or more.

The main limitation of the analysis is likely to be the power of the analysis to detect significant treatment effect modifiers. Our exploratory analyses suggested that country (US vs. non-US) may be predictive of relative treatment effects: We hypothesise that some of this effect may be attributable to other systematic differences between trials conducted in different geographies, and that some may be attributable to patients with a low-normal body mass index being at higher risk of both heart failure death and sudden cardiac death[117;121;122]. Further research is required to confirm this hypothesis. However, if it is correct it would suggest that patients in the UK may experience a stronger benefit from the devices. All future trials in heart failure should collect baseline data on both height and weight. Our analyses also suggested some impact of LVEF on the relative treatment effect of CRT-D; however, the lack of consistency in the impact of LVEF on relative treatment effects across devices make this an area of uncertainty.

It should be noted that the power of this analysis to detect treatment effect modifiers is likely to be low for relatively modest effect modifiers.

Further work to ascertain whether a competing risks framework would be a viable and preferred approach in this context is warranted.

The trial data on which this analysis is based extends to 7.5 years. The treatment effect beyond this point is therefore uncertain. Given this, additional published long term follow-up data were reviewed in order to establish the durability of the device treatment effects. Two trials reporting extensive long-term follow-up were identified in the literature: CARE-HF; and MADIT II, only one of which was in the public domain at time of submission preparation[102]. These studies are discussed in detail in section 3.9.

For the cost-effectiveness modeling we have therefore used the hazard ratios estimated from the network meta-analysis for a period of 7.5 years (the maximum follow-up included in the network meta-analysis). Beyond this period we have assumed that the hazard ratio converges to 1.0 linearly over a 20 year period.

4.7 All cause hospitalisation

4.7.1 Data availability

Data were available from 11 of the 13 clinical trials for the purpose of this analysis.[8;39;43;48;49;51;60;64;67;80;83] In general, information is available for all interventions across all disease severity groups in the first year. Longer term data are dominated by patients with mild heart failure and/or those in receipt of either an ICD or no treatment.

4.7.2 Analyses performed

Hospitalisation can be modelled in one of two ways: expected number of events per month or expected number of days per month spent in hospital. For completeness, we have included both in the economic model, with the number of events per month forming the base case approach and days per month a sensitivity analysis (on the basis that the latter may be associated with greater across-country variability).

For each of the two approaches, a common strategy is used:

i) Estimate the baseline rate (i.e. as experienced by patients on OMT) using baseline clinical parameters as explanatory variables.

ii) Estimate the device specific treatment effect using all available data and clinical parameters as treatment effect modifiers.

In order to avoid double counting of events we have removed all hospitalisation events that occurred in the 60 days post randomisation, as these are accounted for separately in the economic model. (see section 5.5.3). In order to align the results of the hospitalisation analyses with those from the mortality analyses, information was only included for all patients who were not censored for any reason (death, device explant, trial mandated crossover, etc.).

All analyses were performed in STATA v.12 (StataCorp, College Station, TX: StataCorp LP), and accounted for intra-patient correlation and included time as a covariable.

4.7.3 Estimation of baseline hospitalisation rate (rate with OPT)

4.7.3.1 Methods

Given that the data are count data, the conventional regression based approaches[123;124] used to predict events by a range of clinical covariates are as follows:

- Poisson regression (PRM)
- Negative binomial regression (NBRM)

The covariates of interest are those used in the mortality analysis (section 4.1) with the exception of LBBB which was not expected to modify hospitalisation rates and also baseline age (defined as a continuous variable as this was considered a likely predictor of hospitalisation). Goodness of fit was assessed via the Bayesian Information Criteria (BIC), Aikaike Information Criteria (AIC) and two times log-likelihood score (2LL). The selection of final clinical parameters was made via a stepwise process using a cut-off threshold of 0.05 for inclusion. NYHA class was described as having three rather than the conventional four categories (I and II were pooled), because of data scarcity in patients classified as NYHA class I.

Regardless of which goodness of fit criterion was used, the NBRM model was deemed a better fit to the data than the PRM model. The final model used is described in Table 40. A comparison of the observed and predicted values is presented in Figure 20.

Table 40: NBRM results used to predict all cause hospitalisation in OPT arm (baseline risk)

Covariable	βCoefficient	Std. error	Z score	e^β
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	[redacted]	[redacted]	[redacted]	[redacted]
QRS 120-150ms	[redacted]	[redacted]	[redacted]	[redacted]
QRS >150ms	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

Figure 20: Comparison of observed vs. fitted baseline hospitalisation rates (events per month)

[redacted]

4.7.3.2 Results and discussion

The derived monthly probabilities are shown in Table 41, using an assumed starting age of 66 (the average age across all studies included in the hospitalisations analysis).

Table 41: Monthly probability of hospitalisation by covariate pattern (OPT)

	NYHA I/II	NYHA III	NYHA IV
	Non-Ischaemic aetiology		
QRS <120ms	[redacted]	[redacted]	[redacted]
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]
	Ischaemic aetiology		
QRS <120ms	[redacted]	[redacted]	[redacted]
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]

The previous appraisal of ICDs by Buxton *et al*.[33] did not report hospitalisation rates, so it is not possible to compare the results of our analysis with those

previously used. However, it is possible to compare the derived NYHA class III/IV rates for OPT, CRT-P and CRT-D with those previously derived. Fox *et al*.[34] used 28 day values of HF related hospitalisation of 3.81% for OPT. These results should be interpreted with care as the values are based on historical CRT trials conducted in patients who were mostly NYHA class III and had a QRS complex ≥150ms. Ischaemic aetiology was also an inclusion criterion in some of these studies. The results presented in Table 41 also correspond to rates over a slightly longer period (30.44 days [a calendar month] as opposed to 28 days) and are for all cause as opposed to HF related hospitalisation.

Nonetheless, comparison of the values for QRS ≥120ms and NYHA class III/IV with the OPT values in Fox *et al*.[34] demonstrates that the values generated are in line with those used in the previous NICE appraisal.

The value of the present analysis lies in its quantification of risk in patients with both more and less severe HF than previously used, and also the inclusion of age related differences in hospitalisation. In particular, the derived value for patients with the worst possible covariate pattern (NYHA class IV, QRS duration ≥150ms and ischaemic aetiology) is approximately twice that used in the previous appraisal.

Corroborative evidence for the plausibility of this result can be drawn from a recently presented analysis of data elicited from patients with NYHA class III/IV heart failure, mitral regurgitation and a general poor prognosis.[125] While not directly comparable, these patients can be thought of as at high risk of hospitalisation, and the derived monthly value in this patient group was approximately 8.5%.

4.7.4 Estimation of treatment effect on hospitalisation rate

4.7.4.1 Methods

The underlying approach used to estimate the impact of treatment on the rate of hospitalisation is similar to that used in a fixed effects network meta-analysis. Briefly, study specific intercepts were included as well as device related main effects. We also included NYHA class, ischaemic aetiology and baseline age as potential treatment effect modifiers, and explored whether the interaction between either NYHA class or ischaemic aetiology and choice of device had a significant impact on hospitalisation.

Choice of modelling approach was again made using BIC, AIC and 2LL scores, and variables were included at a significance level of P=0.05. Since the underlying data were still count data, the approaches assessed were again PRM or NBRM.

As with the baseline risk, the most appropriate approach to modelling the data was the NBRM. The final model used, after removal of all irrelevant covariates (study intercepts, main effects where interactions are included, etc.) from the table is presented in Table 42.

Table 42: Negative binomial model used to predict the impact of treatment on all cause hospitalisations per month

Covariable	βCoefficient	Std. error	Z score	e^β
Device = ICD	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-P and NYHA = III	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-P and NYHA = IV	[redacted]	[redacted]	[redacted]	[redacted]

Of note, the interaction terms relating to treatment and ischaemic aetiology were not significant and hence, while predictive of baseline risk, aetiology grouping has no significant impact on treatment efficacy.

4.7.4.2 Results and discussion

The derived treatment effects are presented in Table 43.

Table 43: Derived all cause hospitalisation treatment effects

	NYHA I/II	NYHA III	NYHA IV
ICD	[redacted]	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]	[redacted]

Despite information being available from a number of trials in a large number of patients, the results presented above require careful interpretation. In particular, in the underlying data set there were very few patients with NYHA class I/II who

received a CRT-P device, and a small number who were NYHA class IV (particularly amongst patients randomised to ICD). In line with the overall submission strategy we have therefore not generated results for these devices in these patient groups.

Clinically, it is highly unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both receive CRT therapy. In addition, as noted above, the majority of studies from which data were drawn are ICD/CRT-D studies, where the primary endpoints related to mortality and not hospitalisations. It is therefore conceivable that events were either not reported or incompletely recorded in these trials, leading to increased noise in the underlying dataset. This result is therefore highly likely to be a construct of the data used, and clinically plausible assumptions will be made in the model to reinstate face validity. The values used in the model, together with the justification, are presented in Table 44.

Table 44: All cause hospitalisation treatment effects used in the model (events per month)

	Value	**Justification**
		ICD
NYHA I/II	[redacted]	Results from IPD analysis clinically plausible
NYHA III	[redacted]	Results from IPD analysis clinically plausible.
NYHA IV	N/A	Device not assessed in this patient group
		CRT-P
NYHA I/II	N/A	Device not assessed in this patient group
NYHA III	[redacted]	Results from IPD analysis clinically plausible
NYHA IV	[redacted]	Results from IPD analysis clinically plausible
		CRT-D
NYHA I/II	[redacted]	Results from IPD analysis clinically plausible
NYHA III	[redacted]	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)
NYHA IV	[redacted]	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)

4.7.4.3 Device specific values used in the model

The full list of monthly transition probabilities used in the model for each intervention is presented in Table 45 to Table 47. An assumed starting age of 66 was again used in all calculations.

Table 45: Monthly all cause hospitalisation transition probabilities (ICD, events per month)

	NYHA I/II	NYHA III	NYHA IV
	Non-ischaemic aetiology		
QRS <120ms	[redacted]	[redacted]	N/A
QRS >120ms, ≤150ms	[redacted]	[redacted]	N/A
QRS >150ms	[redacted]	[redacted]	N/A
	Ischaemic aetiology		
QRS <120ms	[redacted]	[redacted]	N/A
QRS >120ms, ≤150ms	[redacted]	[redacted]	N/A
QRS >150ms	[redacted]	[redacted]	N/A

Table 46: Monthly all cause hospitalisation transition probabilities (CRT-P, events per month)

	NYHA I/II	NYHA III	NYHA IV
	Non-ischaemic aetiology		
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	N/A	[redacted]	[redacted]
QRS >150ms	N/A	[redacted]	[redacted]
	Ischaemic aetiology		
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	N/A	[redacted]	[redacted]
QRS >150ms	N/A	[redacted]	[redacted]

Table 47: Monthly all cause hospitalisation transition probabilities (CRT-D, events per month)

	NYHA I/II	**NYHA III**	**NYHA IV**
	Non-ischaemic aetiology		
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	[redacted]	[redacted]	[redacted]
QRS >150ms	[redacted]	[redacted]	[redacted]
	Ischaemic aetiology		
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	[redacted]	[redacted]	[redacted]
QRS >150ms	[redacted]	[redacted]	[redacted]

Comparison of the derived values with those used in previous NICE appraisals is again only possible for CRT-P and CRT-D. In their 2007 model, Fox *et al*.[34] used a common four weekly value of 2.49% for heart failure related hospitalisations for both devices. This was derived using relative risk estimates based on data from up to five studies at different time points, but without any correction for the different follow up periods.

Nonetheless, when an assumed 90%/10% distribution of NYHA III/IV is made (the approximate mix of all trials included in the Fox *et al.*[34] model and applied to the non-ischaemic values for the widest QRS duration, again in line with historical trials) the pooled monthly estimate would be [redacted] Hence, allowing for different units of time, the all cause hospitalisation values derived using the IPD based approach are very similar to the HF hospitalisation related values used in previous appraisals.

4.7.5 Conclusions from the IPD analysis of all cause hospitalisation

The significant ($p<0.05$) predictors of hospitalisation in patients on OMT were NYHA class, aetiology, age and QRS duration. All of these would be expected *a priori* to impact on hospitalisation, and so our results retain face validity. All three devices were estimated to reduce the rate of hospitalisation. Only NYHA class was found to be a significant effect modifier, and only for the CRT-P device, with patients in higher NYHA classes experiencing a stronger treatment effect. We also used two different approaches to analysing the data, and the results from

both are internally consistent.

Across all NYHA classes, device therapy was associated with a reduction in admission rates.

In NYHA class I to III, ICD was associated with a [redacted] reduction in admission rates, and CRT with a [redacted] reduction. The effect in NYHA class IV is even more pronounced, with CRT offering a [redacted] reduction in admission rates (although the data used to inform this result are sparse).

A patient who is hospitalised places a burden on local resources and is likely to have a reduction in general well-being. Thus, treatments that reduce hospitalisation will be attractive to both local finance managers and patients.

The key value of the IPD approach used in our analysis is that it allows results to be generated for a range of clinical variables. This in turn allows for a more nuanced approach to identifying clinical benefit. By virtue of working with data from multiple clinical trials, we are also able to identify any benefits that would not have been identifiable had a single study been used. We were also able to identify and correct for any placebo or Hawthorne effects inherent in the clinical trial data.

Because of the level of data available and the ability to use clinical and patient characteristics to define the admission rate, the results from this analysis are the best and most robust currently available. The data were completely aligned with the mortality analysis, and so derived event rates were based on the same follow up data as survival rates.

That our results are more nuanced and more useful in terms of medical decision making can be seen by comparing them with those from the previous CRT appraisal. The latter generated pooled event rates for patients who were NYHA class III/IV, and did not account for ischaemic aetiology. The monthly values from the “worst case scenario” in the current analysis are nearly twice those from previous analyses, meaning that the previously generated rates were not reflective of what is actually happening in clinical practice.

4.8 Health related quality of life

The purpose of this analysis is to inform the utility values used in the economic model. It is useful first to briefly review values used in other models. We then present the modelling methods used, followed by the results and conclusions from the HRQoL analysis (see Section 4.8.9).

4.8.1 Review of results from the literature review

The review of published HRQoL data (Section three) is highly supportive of the following hypotheses:

i) The impact of treatment is dependent on whether an individual is classified as NYHA class I/II or NYHA class III/IV.

ii) Use of an implanted CRT device significantly improves HRQoL in patients with severe HF.

iii) Use of an ICD device neither significantly improves nor worsens HRQoL of patients with severe HF.

iv) The impact of CRT therapy in patients with mildly symptomatic HF is more modest than in severe HF, possibly due to a ceiling effect, and there may be no differences between device types in impact on HRQoL in these patients.

The economic model from the previous NICE appraisal of CRT used NYHA class specific utility scores.[34] Our review of the impact of treatment on the underlying disease (expressed as either change in NYHA score from baseline or improvement in NYHA class), when used in combination with the NYHA specific utility scores, further supports these hypotheses.

4.8.2 Overview of values used in previous models

As mentioned above, in their submission dossier to the previous CRT appraisal, PenTAG used NYHA class specific utility values, which were combined with the results from the CARE-HF trial to estimate the change in utility over time.[34] In contrast, in the original assessment of ICD therapy Buxton *et al.*[33] used a common utility score for ICD and OPT (0.75), with the rationale being ‘based on UK sample data’.

Among the non-UK HTA based models, the values used for each intervention in a selection of studies are summarised in *Table 48*. Although not a systematic review of the literature, trends emerge from the information provided, principally that ICD and OMT have commonly been assumed to have the same impact on an individual's health related quality of life.

Table 48: Overview HRQoL modelling approaches used in previous economic models

Study	Interventions	Method used
Calvert *et al.*[126]	CRT-P, OPT	Advanced statistical techniques and mapping algorithm used to derive treatment specific long term utility scores
Feldman *et al.*[127]	CRT-P, CRT-D, OPT	Derived via a mapping algorithm applied to MLWHF scores
Al-Khatib *et al*.[128]	ICD/ OPT	Common value of 0.88 used for both interventions. Source unstated in text
Linde *et al.*[129]	CRT, No CRT	Trial based analysis of NYHA mix over time combined with PenTAG NYHA values
Mark *et al.*[130]	ICD, OPT	A common utility weight of 0.85 was used for both treatments based on a regression analysis of time trade off data
Sanders *et al.*[131]	ICD, OPT	Common value of 0.88 applied to both treatments
Yao *et al.*[132]	CRT-P, CRT-D, OPT	NYHA class specific utility scores

4.8.3 Overview of approach used in current model

The approach used in the current model is as follows:

i) Estimate UK specific age and gender population utilities.

ii) Derive a disease specific decrement using the patient level EQ-5D data, with a range of clinically plausible variables used to parameterise the regression equation. The derived decrements will be compared to the population norms in order to derive an estimate of the impact of disease beyond natural background ageing in different subgroups.

iii) Derive treatment specific increments associated with each device at first follow up visit by NYHA class. For the purposes of this model we have used an NYHA codification of I/II, III and IV.

iv) Estimate the period of time over which the benefit of treatment is experienced. Individuals will experience a tailing off in treatment related benefit up to this point and thereafter will revert to baseline (OMT) utility (i.e. no benefit).

Point iv) is where the current approach differs from all previous analyses. As can be seem from Section 4.4.2, all other researchers, even those using regression based approaches, have assumed that the benefit of treatment is constant over time. In previous NICE appraisals, the time horizon used in the ICD model was 20 years, with the constant utility applied in all years. In the CRT appraisal, the NYHA mix at 18 months was assumed to hold in all future cycles. Hence, the current approach is more conservative than any previous analysis.

Despite patient level MLWHF data being available in multiple trials at multiple time points, we chose not to use these for any of the primary HRQoL analyses. The rationale for this decision was two-fold. Firstly, as noted in the most recent version of the NICE reference case, there is a strong desire for preference weights to be derived using the EQ-5D instrument[103]. The second reason was the criticisms raised during the previous NICE appraisal of CRT of the mapping algorithm devised by Havranek *et al*.[133], in particular its poor predictive accuracy (R^2=0.1). Similarly, a multiple imputation approach such as used by Calvert *et al.* in the previously published CARE-HF model[126] was rejected due to inadequate imputation accuracy arising from high levels of missing data in the dependent variable. The level of data for the key variable (EQ-5D) was “block missing” (i.e. not collected in most studies from which data were available).

Nevertheless, we have analysed the MLWHF data, with a view to using the results to support any modelling assumptions made, and in particular to estimate the duration of treatment benefit.

Each of the four components of the base case analysis is discussed separately below.

4.8.4 Modelling EQ-5D population preference weights

The key data source for estimating UK specific age and gender EQ-5D population norms is a study by Kind *et al.* of 3,395 individuals resident in the UK.[134] The raw data are reproduced in Table 49 and the results of regression equations using the mid-point of these ranges as the time variable are presented in Table 50. The

values were used to generate all population estimates in all model cycles.

Table 49: Age and gender specific UK EQ-5D population norms (mean, SD.) reproduced from Kind et al. [134]

Age band	Male	Female
Under 25	0.94 (0.12)	0.94 (0.12)
25-34	0.93 (0.16)	0.93 (0.15)
35-44	0.91 (0.17)	0.91 (0.15)
45-54	0.84 (0.27)	0.85 (0.23)
55-64	0.78 (0.28)	0.81 (0.26)
65-74	0.78 (0.28)	0.78 (0.25)
75+	0.75 (0.28)	0.71 (0.27)

Table 50: Regression coefficients used to model age specific population utility

	Coefficients			
Group	**Constant**	**Age**	**Age squared**	**R^2 statistic**
Male	1.0257	-0.0036	N/A	0.9413
Female	0.9643	-0.0002	-0.00004	0.9872

4.8.5 Estimating the impact of baseline disease severity on HRQoL

EQ-5D data were available from three studies for the purpose of this analysis (N=4,432).[8;67;80] The raw data are presented graphically in Figure 21 and the distribution of individuals across the NYHA groups is shown in Table 51.

Figure 21: Histogram of baseline EQ-5D data across all three clinical trials

[redacted]

Table 51: Distribution of baseline EQ-5D observation counts by NYHA class

Class	Count	Percentage of total
I/II	[redacted]	[redacted]
III/IV	[redacted]	[redacted]

A large number of individuals [redacted] reported a score of 1 (implying perfect health), and the majority of the individuals in whom EQ-5D data were collected had mild to moderate heart failure (see Table 51). In order to derive decrements, the data were transformed to a proportional change from unity (see Figure 22). Since the transformed data are in count format, standard regression techniques can be applied to estimate the impact of different baseline clinical variables on HRQoL.

Figure 22: Histogram of baseline EQ-5D data across all three clinical trials expressed as proportional change from unity

[redacted]

The regression techniques introduced in Section 4.7.3 (modelling of hospitalisation) were assessed for candidacy, with a negative binomial model being used in the final analysis. The justification for this choice is presented in Appendix 12.

The final negative binomial model is presented in Table 52. Variable selection was again made on the basis of stepwise methods using an inclusion threshold of 0.05.

Table 52: NBRM Coefficients used to predict baseline utility decrement

Covariable	βCoefficient	Std. error	Z score	e^β
NYHA = III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA = IV	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	[redacted]	[redacted]	[redacted]	[redacted]
Gender= Male	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

* Variable included despite not being significant on the basis of the underlying disease. Lack of significance likely to have arisen due to small patient counts.

Validation

Due the combination of treatment options, clinical variables and time, as well as the distribution of patients across the covariate patterns, the analysis of patient level EQ-5D data was particularly challenging, and interpretation of the model outputs is not straightforward. Validation of the approach is also challenging, since all of the available data have been used in the construction of the model. Nevertheless, generating results for all patient covariate patterns allows for a simple sanity check. Non-ischaemic subgroups are presented in Table 53 and ischaemic subgroups in Table 54. A common assumed starting age of 66 has been used in all calculations, giving an average age and gender adjusted UK population norm utility score of 0.7902 for females and 0.7900 for males.

Table 53: Comparison of indicative individuals with population equivalents (non-ischaemic aetiology)

		Decrements from unity		
NYHA	Gender	Pop Norm	Derived	Disease specific component*
I/II	Male	0.2100	[redacted]	[redacted]
I/II	Female	0.2098	[redacted]	[redacted]
III	Male	0.2100	[redacted]	[redacted]
III	Female	0.2098	[redacted]	[redacted]
IV	Male	0.2100	[redacted]	[redacted]
IV	Female	0.2098	[redacted]	[redacted]

* Corresponds to difference between population norm and derived value. To be interpreted as the impact of disease above and beyond what would naturally occur.

Table 54: Comparison of indicative individuals with population equivalents (ischaemic aetiology)

		Decrements from unity		
NYHA	Gender	Pop norm	Derived	Disease specific component*
I/II	Male	0.2100	[redacted]	[redacted]
I/II	Female	0.2098	[redacted]	[redacted]
III	Male	0.2100	[redacted]	[redacted]
III	Female	0.2098	[redacted]	[redacted]
IV	Male	0.2100	[redacted]	[redacted]
IV	Female	0.2098	[redacted]	[redacted]

* Corresponds to difference between population norm and derived value. To be interpreted as the impact of disease above and beyond what would naturally occur.

Broadly speaking, and allowing for the relatively complex approach used as well as the nature of the underlying data the following general statements appear to hold in relation to the derived values:

i) The size of the disease specific decrements increases through the NYHA classes.

ii) Individuals in NYHA class I/II have effectively the same HRQoL as an age equivalent member of the general public.

iii) Patients with ischaemic aetiology have a slightly worse HRQoL than those with

non-ischaemic aetiology.

iv) Slight differences exist between the values generated for males and females.

Overall, this is all what would be expected given the nature of the underlying disease. A simpler validation is to compare the decrement-derived absolute EQ-5D values with the raw, mean EQ-5D data from the three trials that collected it. A summary of the relevant trial information is presented in Table 55. Absolute values for each covariate combination range from approximately 0.8 for patients who are in NYHA class I/II to approximately [redacted] for those who are in NYHA class IV and have an ischaemic aetiology of heart failure.

Table 55: Summary EQ-5D statistics from the three clinical trials in which data was collected

Study	N	Mean	Std. Dev	Min	Max
CARE-HF	741	0.6031	0.28204	-0.59	1.00
MADIT-CRT	1787	0.7958	0.19214	-0.43	1.00
RAFT	1789	0.7512	0.19492	-0.145	1.00

The derived absolutes are within an acceptable level of tolerance for inclusion into the three studies, though again the external value of this comparison is limited due to the comparison of results from a regression analysis with the input data. However, it does show that the zero inflated negative binomial model has internal validity.

Overall, the approach used generates clinically plausible results.

4.8.6 Estimating impact of treatment on HRQoL

EQ-5D data were used in the HRQoL analysis, but the EQ-5D instrument was used in only three of the trials. For this reason, it was felt appropriate to refer to the larger MLWHF data set to corroborate the results in those instances where clinically counter-intuitive results were generated for particular subgroups.

The impact of treatment on a patient level can be calculated as the difference between baseline and first follow up period (with the 90 day data from CARE-HF assumed to reflect what would have been observed at 180 days, the follow-up available for the other trials). As discussed in section three of the review of clinical efficacy, the impact of treatment is likely to depend on NYHA class and

the choice of treatment. In total 3,736 observations were available to inform the analysis.

As highlighted in Table 51, the majority of individuals are in NYHA I/II at baseline. Further confounding variables are that two of the four treatment options (ICD and CRT-D) are only used in RAFT and MADIT-CRT, and the other two exclusively used in CARE-HF. Furthermore, when device use is viewed by NYHA group, only [redacted]. Hence, there is a weak network of studies available to inform any meaningful regression analysis.

We have therefore used the IPD data to generate mean changes from baseline for each device type by NYHA group. The results are presented in Table 56. Results for ICD in patients who are NYHA IV and CRT-P in patients who are NYHA I/II have not been generated.

Table 56: Mean changes from baseline in EQ-5D at six months by device and NYHA group (mean, s.e.)

	NYHA = I/II		NYHA = III		NYHA = IV	
	N	Change	N	Change	N	Change
OPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Significant at 95% confidence level

The results for several patient groups appear highly counter-intuitive given the nature of the underlying disease and the interventions being used. Most obvious of these are the results for all NYHA IV patients, and for CRT-D in NYHA III. The latter are particularly striking given the positive results for CRT-P in the same patient group and the use of a common treatment component.

4.8.6.1 Exploratory analysis: change in MLWHF at 6 months

In order to assess whether or not the counter-intuitive results are real or artefacts of the EQ-5D data and modest patient counts, an identical analysis was performed for all MLWHF data. The results from this analysis are presented in

Table 57.

Table 57: Mean changes from baseline in MLWHF at six months by device and NYHA group (mean, s.e.)

	NYHA = I/II		NYHA = III		NYHA = IV	
	N	Change	N	Change	N	Change
OPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall, far more data were available for this analysis than for the analysis of EQ-5D data. Assuming that MLWHF is a fair representation of an individual's health related quality of life the following conclusions can be drawn:

i) The impact of CRT-D and CRT-P on HRQoL in patients who are in NYHA class III or NYHA class IV is both substantial and very similar.

ii) CRT-P has at least as large an impact on HRQoL in patients who are in NYHA class I/II as either ICD or CRT-D.

iii) Regardless of NYHA class, individuals who do not get any form of device achieve at best a modest change in HRQoL.

This last point suggests that some form of placebo effect, or continuing improvement due to OPT is occurring, meaning that a correction needs to be made to all values used for all devices to ensure that this effect is not included (i.e. a 'difference in difference' approach is required).

4.8.7 Values used in the model

On the basis of the above analyses of six month data, as well as information presented in the systematic review section of the dossier, the values used in the model and the justification for the choices are presented in Table 58. In generating these values, we have deducted the OMT NYHA class III value from all estimates (see Table 56) to account for any trial based placebo effects. In effect, we have used a difference in differences approach to generating the final values used.

Table 58: Treatment specific utility increments used in the economic model

	Value	Justification
		NYHA = I/II
OPT	[redacted]	No clinical reason why an individual already on optimized medication would have a change in utility
ICD	[redacted]	Value derived from IPD analysis [redacted]. Systematic review highly suggestive of ICD therapy have a positive impact in this patient group
CRT-P	[redacted]	Cost-effectiveness results not generated for this treatment option
CRT-D	[redacted]	Value derived from IPD analysis [redacted]. Systematic review and MLWHF analysis highly suggestive of CRT-D therapy have a positive impact in this patient group
		NYHA III
OPT	[redacted]	No clinical reason why an individual already on optimized medication would have a change in utility
ICD	[redacted]	Result from IPD analysis not significantly different to zero. Literature review supportive of no benefit from ICD treatment in this patient group
CRT-P	[redacted]	Value derived from IPD analysis [redacted]. Literature review concluded that there was a benefit of this treatment option in this patient group, supported by MLWHF analysis
CRT-D	[redacted]	Assumed same as value used for CRT-P. IPD results for this treatment option derived from very small patient numbers. No clinical reason why this should perform any different to CRT-P. Analysis of MLWHF and literature review strongly supportive of therapeutic benefit in this patient group
		NYHA IV
OPT	[redacted]	No clinical reason why an individual already on optimized medication would have a change in utility
ICD	[redacted]	Cost-effectiveness results not generated for this treatment option
CRT-P	[redacted]	Not enough information available to inform meaningful analysis. Assumed same as for NYHA III. Analysis of MLWHF data supportive of this assumption
CRT-D	[redacted]	Not enough information available to inform meaningful analysis. Assumed same as for NYHA III. Analysis of MLWHF data supportive of this assumption

4.8.8 Estimation of HRQoL treatment benefit duration

4.8.8.1 Relevant long term published data

In a long term retrospective analysis of the CARE-HF HRQoL data, Cleland *et al.*[56] used a previously published algorithm[31] to estimate the magnitude of benefit

at 18 months and study end. The key results are reproduced in Table 59. The observed 3 monthly difference estimate was, unsurprisingly, very similar to that generated using the IPD analysis and was maintained for at least 18 months (the minimum follow up period) until study end. Interpretation of “end of study” is not obvious, but median follow up was 29.6 months. We have thus interpreted the results as saying that the benefit lasted for at least 2.5 years.

Table 59: CARE-HF based long term EQ-5D gains (mean, 95% CI) reproduced from Cleland et al. [56]

Time point	OPT	CRT-P	Difference	P-value
Baseline	0.60 (0.57, 0.63)	0.60 (0.58, 0.63)	N/A	N/A
3 months	0.61 (0.59, 0.64)	0.69 (0.66, 0.72)	0.08 (0.04, 0.11)	<0.0001
18 months	0.52 (0.48, 0.54)	0.61 (0.58, 0.64)	0.10 (0.06, 0.15)	<0.0001
End of study	0.43 (0.39, 0.46)	0.56 (0.52, 0.59)	0.13 (0.08, 0.18)	<0.0001

4.8.8.2 Additional IPD analyses

Long term MLWHF data from all studies and all devices was used to inform change from baseline estimates at three-monthly periods, and as a conservative assumption it was decided to limit the duration of treatment benefit on HRQoL. More technically, we identified the time point at which the mean change from baseline was zero. The purpose of this analysis was to estimate how far beyond 2.5 years treatment related HRQoL benefit might exist.

In general, not enough data in patients who were in NYHA class IV were available to inform a meaningful analysis. Similarly, minimal data existed for CRT-P patients post 18 months in all NYHA classes, so again no meaningful long term analysis could be performed. The ‘difference in difference’ values for NYHA class I/II and NYHA class III for ICD and CRT-D (mean device value minus mean OMT value) are plotted in Figure 23 and Figure 24. With the exception of ICD in NYHA I/II, benefit is still being experienced (on average) [redacted] years after device insertion

Figure 23: difference in difference (device-OPT) long term change in MLWHF (NYHA I/II)

[redacted]

Figure 24: difference in difference (device-OPT) long term change in MLWHF (NYHA III)

[redacted]

4.8.8.3 Value used in model

In order to be conservative in our assumptions we have assumed a health related quality of life benefit of five years for all devices in all NYHA classes.

The impact of truncating this benefit period is explored in sensitivity analyses.

4.8.9 Conclusions from the HRQoL analysis

In our analysis of the EQ-5D data, after accounting for placebo effects, CRT had a strong impact on HRQoL [redacted] in NYHA class I/II; [redacted] in NYHA class III/IV).

There was a small positive impact of ICD for patients in NYHA class I/II [redacted], but not for patients in NYHA class III/IV (hence, any extension of life in these patients will have the same HRQoL as would be observed on OPT.

The key clinical parameters that had a significant ($p<0.05$) impact on baseline HRQoL were NYHA class, aetiology, age and gender. Of these, NYHA class is a surrogate for disease severity, and aetiology status a proxy for previous MI. In addition, age and gender are known modifiers of HRQoL in the general population. Hence, the results have face validity. However, the direction of impact of age and gender is opposite to what would be expected in the general population, albeit very slightly. This should be viewed as a limitation of the analysis and is reflective of the data used and not the analytical approach.

From the patient perspective, improvements in quality of life are arguably as important as life extension. As noted in Section 3.7, individual studies showed significant HRQoL improvements regardless of whether a generic (EQ-5D) or disease specific (MLWHF) instrument was used. These studies report results at the aggregate level (i.e. for all patients in a study) and not at a patient level.

The benefits of the IPD based approach for estimating treatment effects on HRQoL are similar to those discussed for all cause hospitalisation. Again, the HRQoL analysis is completely aligned with the mortality data, meaning that the same patient exposure data were used. Hence, the results presented here represent the best, most robust evidence as to the magnitude of HRQoL benefit for each intervention.

Interestingly, while no direct mapping algorithm exists to generate EQ-5D preference weights solely from MLWHF scores, the IPD analyses of data for this disease specific instrument can be used to inform the duration of HRQoL benefit.

- In patients who were in NYHA class I/II and had ICD based treatment,

improvement in MLWHF existed for approximately [redacted] years (contingent on the individual being alive).

- In patients who were in NYHA class III/IV, contingent on being alive, the duration of benefit was approximately [redacted] years.

Hence, our analyses show that HRQoL benefits are likely to be maintained for many years after initial implant. This result is in line with recently published information from the CARE-HF study.

5 Assessment of cost-effectiveness

- This section presents the methods and inputs used to model cost-effectiveness.
- The modelling approach used is described. Note that full details of the methods used to model mortality, hospitalisation and HRQoL are described in Section 4.
- The values used in the model are presented, along with explanations of how they were sourced or derived.
- Long term (>10 year) time to device replacement data from approximately 40,000 UK implants was used to inform device failure rates for all three interventions. Predicted median time to replacements for ICD, CRT-P and CRT-D are 7.1, 10.3 and 5.8 years respectively.
- We have used conservative assumptions throughout. In particular, in contrast to previous models, we have assumed that any treatment effects on mortality or HRQoL are not constant but diminish over time.
- Initial implant costs for ICD, CRT-P and CRT-D are £15,248, £8,281 and £17,849 respectively.

5.1 Description of modelling approach

The model has two ‘health states’: alive and dead. The rationale for this approach is that, in the patient population of interest, death is the main clinical event. By modelling death directly via a series of covariate based regression equations (for baseline risk and treatment effect), we were able to use the long term data available and to explore the impact of patient-level heterogeneity. This approach also allowed for a coherent regression-based approach to modelling HRQoL and all-cause hospitalisation that was aligned with the mortality analysis. Of the other approaches to modelling HRQoL that we considered, the use of a clinical surrogate (i.e. time-dependent progression through NYHA classes) was rejected due to the technical difficulties it would entail, as well as the loss of predictive accuracy.

The first regression equation is used to predict the probability of death in patients who receive OMT but no device, based on a range of clinical covariates. These probabilities are used in combination with treatment effects derived via network meta-analyses to derive device specific death probabilities. The methods used to define this approach are described in detail in section 4.2

Conditional on being alive at a given time point, two additional equations are used to predict the probability of experiencing a hospitalisation event, and the level of HRQoL (utility). The methods used are described in detail in section 4.3 and section 4.4. In addition, all living patients potentially incur other costs related to device replacement, background medication and routine clinical visits.

The analysis follows NICE methodological guidance issued in 2008.[103] A lifetime time horizon has been used for the model in combination with a one month cycle length, and all costs and benefits (QALYs) incurred or accrued for each treatment option are calculated. Annual discount rates of 3.5% and a half cycle correction are applied to both costs and benefits in all calculations. A strict UK NHS perspective has been used in all cost calculations.

5.2 Mortality

The method used to model mortality is described in detail in section 4.2

5.3 Event probabilities

5.3.1 All cause hospitalisation

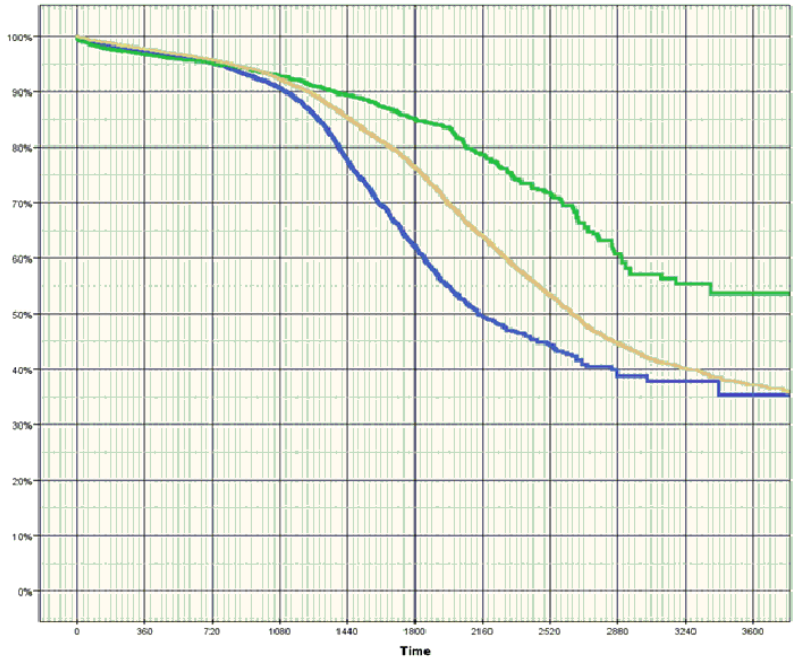
The method used to model all cause hospitalisation is described in detail in section 4.3

5.3.2 Device lifetime (time to first replacement)

UK device longevity estimates were derived from an analysis of all implants with verified life status from 1/1/2000 until 14/4/2011. This was performed on behalf of the Association of British Healthcare Industries (ABHI) by Dr. David Cunningham, Director of the Central Cardiac Audit Database (CCAD) (supplied via personal communication). The results are presented as Kaplan-Meier plots in Figure 25. Approximately 40,000 implants were used to inform the analysis (ICD:22,259 CRT-P:7,968 CRT-D:10,062). The data were uncensored, meaning that all device replacements, however soon after initial implant, were included. Given that CCAD

is run by the NHS Information Centre, and the large number of implants from which data was available, the device longevity estimates represent the best currently available.

Figure 25: UK device longevity data (Jan 2000 to April 2011, time unit: days)



Legend: Blue=CRT-D, Yellow=ICD, Green=CRT-P

In order to include the information in the model, we electronically extracted the above data into Microsoft Excel® (Microsoft Corporation, Redmond, WA) and fitted Weibull parametric functions. No data were excluded from the curve fitting process. The Weibull curve was chosen since it is commonly used to model such data and often offers a good fit (both in terms of within-data accuracy and long term predictive plausibility). In the case where the fitted Weibull curve was deemed unrealistic (i.e. either within data period accuracy was poor or extrapolated survival clinically implausible), a broader range of commonly used functions would be used (exponential, log-normal, log-logistic) and the “best” fit chosen from this wider set.

Comparisons of the observed and fitted Weibull functions for CRT-P and ICD are presented in Figure 26 and Figure 27. The fitted curves were a reasonable approximation with clinical face validity, and no other alternatives were considered. Since the curve fitting process was undertaken in Excel, goodness of fit is assessed via the R^2 statistic (>0.97 for both curves).

Figure 26: Parametric function fitted to UK CRT-P implant data

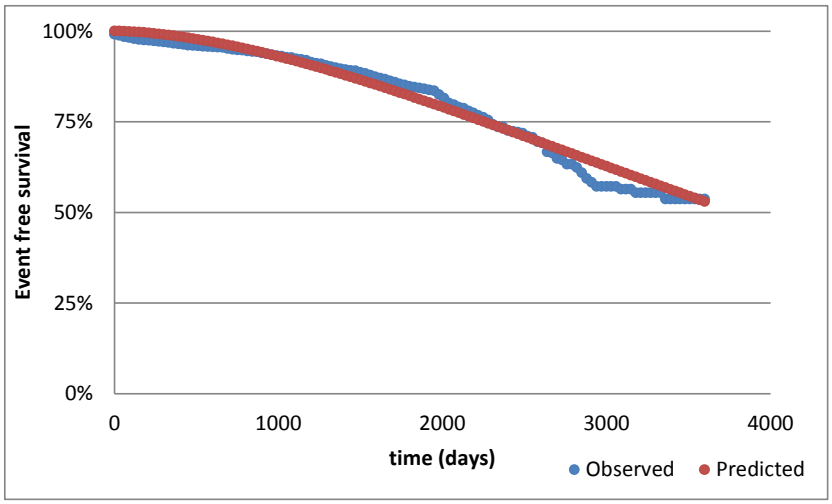
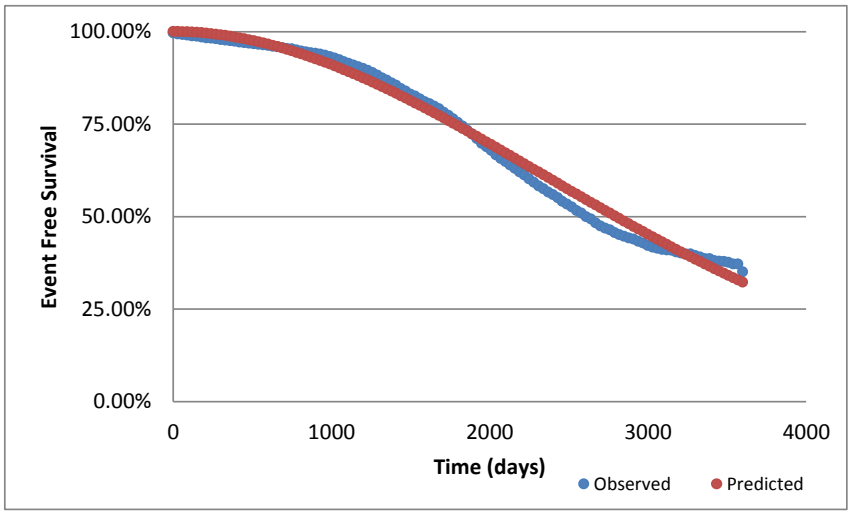


Figure 27: Parametric function fitted to UK ICD implant data



The Weibull curve used to model the CRT-D data was not as good a fit to the data as those used for ICD and CRT-P and so the wider range of curves were fitted. A comparison of the observed CRT-D data and fitted exponential, Weibull, log-logistic and log-normal functions is presented in Figure 28. No curve completely captures the observed data. We also considered, but rejected, a piecewise curve fitting approach since this generated clinically implausible device longevity estimates. Hence, we have used the Weibull function in the base case for reasons of extrapolative plausibility (see Figure 29). Of note, the final choice generates the lowest estimate of mean device longevity, and can therefore be considered conservative.

Figure 28: Parametric function fitted to UK CRT-D implant data

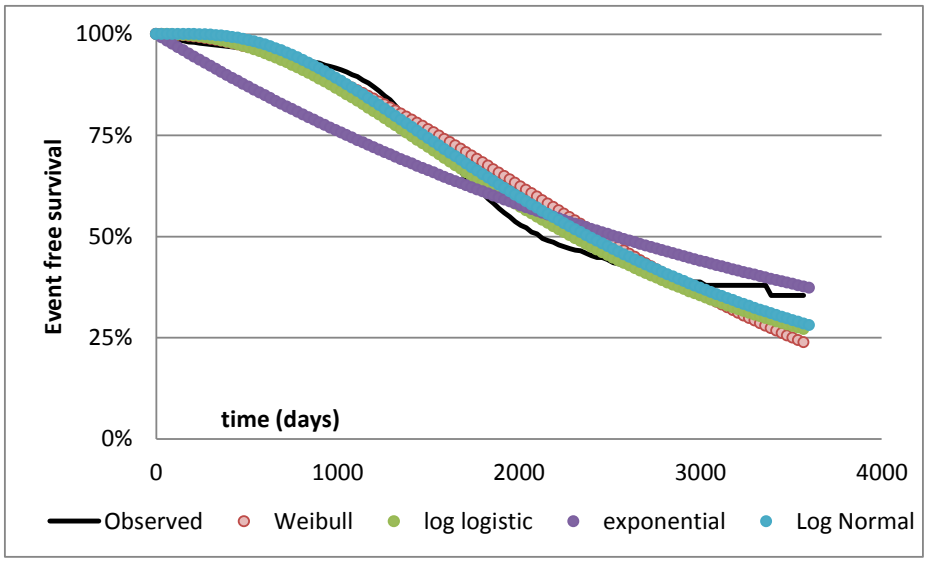
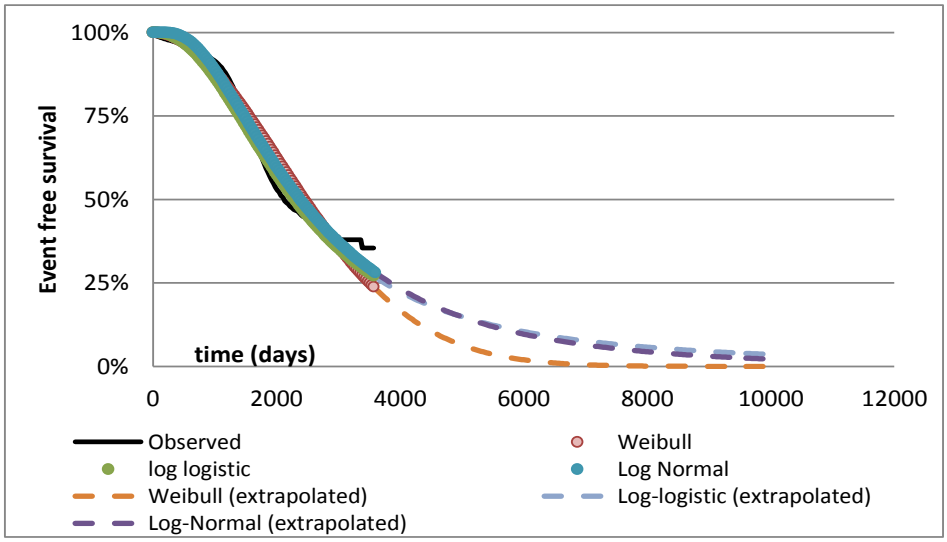


Figure 29: Extrapolation of parametric functions: CRT-D data only



Cycle specific cumulative survival probabilities were used to estimate device specific failure probabilities using conventional formulae.[135] Values were not applied to the first two cycles (i.e. 60 days) in the model because of the approach used to model adverse events.

5.3.3 Device lifetime (time to subsequent replacements)

As can be seen from Figure 25 above, device replacement will be uncommon during expected survival, with the exception of those with mild heart failure. We have therefore assumed, for completeness and given the complexity of the underlying cost-effectiveness model and the need to avoid 'tunnel states' (states where patients can only remain for one cycle), that conditional on having already

had one replacement, the probability of subsequent replacements (i.e. second and subsequent) in any given cycle is constant for each device type. Device specific median survival estimates derived from the Cunningham dataset were used to inform these transition probabilities.

The values used in all model cycles are presented in Table 60.

Table 60: Parameters used to derive time to second and subsequent device replacement estimates

Treatment option	Median time to failure (days)	Derived monthly rate of replacement (second/ subsequent)
ICD	2600	0.00039
CRT-P	3780*	0.00027
CRT-D	2115	0.00047

* Failure curves not crossed 50% value at end of follow up period. Hence, median value from fitted curve used.

5.3.4 Device related adverse events (short term)

The nature of the costing approach used to derive total initial implant costs is based on a mixture of wholesale prices (for devices and leads) and HRG tariffs which cover all additional costs (inpatient care, short term adverse events etc.). Thus, to avoid double counting we have not explicitly included short term device related adverse events separately in the model.

5.3.5 Infection rates (post battery replacement)

Infection following device replacement is a relatively uncommon but serious device-related adverse event, and has therefore been included in the model for all procedures subsequent to the initial implant. The proportion of patients experiencing this event was based on information derived from 1,744 North American individuals who were included in the REPLACE registry.[136] Overall, 14 major events were reported in all generator replacements (0.8%). This value has been applied to all devices in the first cycle following battery replacement.

5.4 Resource use

5.4.1 Reasons for hospitalisation

In a review of 322 incident cases of heart failure in England, Cowie *et al*. noted that 50.1% of subsequent hospitalisations related to worsening heart failure and the remainder are explained by multiple other reasons.[137]

In addition, lead-related complications can be expected to occur in every month and will result in time in hospital. The most up to date information on this event comes from the REPLACE registry. In this database, of the 1,031 individuals without a planned lead related procedure, a total of 11 severe lead related events occurred (1.07%) across all hospitalisations.[138] The proportion of patients hospitalised for reasons other than worsening heart failure or lead related complications is the remainder (100% minus 50.1% minus 1.07%).

A summary of the values by hospitalisation type used in the model is presented in Table 61. As with the derivation of device related adverse events, common logic has been applied to exclude lead related events from patients on OMT. These values are used in combination with the costs presented in Section 5.5 to generate an average cost per hospitalisation event.

Table 61: Distribution of reasons for hospitalisations by intervention

	OPT	**ICD**	**CRT-P**	**CRT-D**
Heart failure related	50.1%	50.1%	50.1%	50.1%
Lead related	0%	1.07%	1.07%	1.07%
Other reasons*	49.9%	48.83%	48.83%	48.83%

* Values calculated as the residual of the other two

5.4.2 Background medication

A summary of the proportion of patients using a range of heart failure medications, by NYHA class, is presented in Table 62. The source for this information is a combination of the clinical studies identified in the systematic review (see Section 3) and expert opinion. Common values are applied to all four interventions in each month of the model (conditional on being alive), on the basis of baseline NYHA values.

Table 62: Background medication by NYHA class

	NYHA I	NYHA II	NYHA III	NYHA IV
Atorvastatin	20%	20%	20%	20%
Simvastatin	55%	55%	55%	55%
Warfarin	10%	15%	25%	40%
Clopidogrel	15%	15%	15%	15%
Ramipril	90%	90%	90%	90%
Carvedilol	85%	85%	75%	70%
Spironolactone	0%	30%	30%	30%
Digoxin	5%	25%	25%	25%
Furosemide	75%	80%	90%	95%
Eplerenone	0%	30%	30%	30%

5.4.3 Other resource use parameters

We have assumed that patients will require bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

5.5 Costs

5.5.1 Optimal pharmacological medical therapy (OMT)

5.5.1.1 Doses used in all calculations

OPT for HF is composed of a range of drugs both for heart failure treatment and primary and secondary prevention. An OPT regimen is taken by all patients, regardless of whether they receive a device in addition. In order to estimate the cost per cycle of pharmacological therapy, we used the British National Formulary (BNF)[139] to find the recommended daily dose for each commonly used drug (Table 63). Where a range of doses was possible, we have used those typically used in routine clinical practice as the basis of all costings.

Table 63: Recommended doses

Drug	Dose (mg/day)	Source
Atrovastatin (Liptor®)	10	British National Formulary[139]
Simvastatin	20	British National Formulary[139] Value represents clinical practice
Warfarin	1	British National Formulary[139]
Clopidigrel	75	British National Formulary[139] Value represents clinical practice
Ramipril	10	British National Formulary[139]
Carvedilol	25	British National Formulary[139] Value represents clinical practice
Spironolactone	25	British National Formulary[139] Value represents clinical practice
Digoxin	125[a]	British National Formulary[139] Value represents clinical practice
Furosemide	60	British National Formulary[139] Value represents clinical practice
Eplerenone	25	British National Formulary[139] Value represents clinical practice

a) Dosing measured in μg and not mg per day

5.5.1.2 Purchase costs for pharmacological therapy

Information on the costs of various combinations of pack size and tablet concentration was available from the BNF (Table 64). An average of these costs was calculated based on the cost per tablet, which was then combined with the mean dose to derive an estimate for the cost per cycle of each drug and the mean monthly cost of pharmacological treatment by NYHA class in (Table 65).

The drug cost allocated in any given month to each patient alive, regardless of treatment option, is predicated on their baseline NYHA class.

Table 64: *Purchase costs*

Drug	Tablets per pact	Tablet dose	Pack price	Source
Atrovastatin (Liptor®)	28	10mg	£13.00	BNF[139]
Simvastatin	28	10mg	£0.90	BNF[139]
	28	20mg	£1.01	
	28	40mg	£1.32	
	28	80mg	£2.29	
Warfarin	28	0.5mg	£1.49	BNF[139]
	28	1mg	£0.93	
Clopidigrel	30	75mg	£3.40	BNF[139]
	28	75mg	£3.17	
Ramipril	28	1.25mg	£1.10	BNF[139]
	28	2.5mg	£1.18	
	28	5mg	£1.25	
	28	10mg	£1.41	
Carvedilol	28	3.125mg	£1.10	BNF[139]
	28	6.25mg	£1.25	
	28	12.5mg	£1.37	
	28	25mg	£1.84	
Spironolactone	28	25mg	£1.55	BNF[139]
	28	50mg	£2.11	
	28	100mg	£2.46	
Digoxin	28	62.5	£2.03	BNF[139]
	28	125	£1.12	
	28	250	£1.13	
Furosemide	28	20	£0.81	BNF[139]
	28	40	£0.84	
	28	500	£4.05	
Eplerenone	28	25	£42.72	BNF[139]

Table 65: Total cost of treatment per 1 month model cycle

	NYHA I	NYHA II	NYHA III	NYHA IV
Total cost per cycle	£14.28	£22.21	£22.13	£22.30

5.5.2 Hospitalisation events

As noted in Section 4, two approaches to estimating all cause hospitalisation were used: mean number of events per month and mean number of days per month. Hence, two different costing approaches are required.

The NHS Schedule of Reference Costs (SRC) provides numerous estimates of the cost of hospitalisation, including those specific to HF patients.[140] These are further subcategorised by whether the admission is elective or non-elective, whether it is an inpatient, outpatient or day case, and whether or not the patient experiences complications.

The cost of a hospitalisation event for HF hospitalisations using EB03H and EB03I was calculated as a weighted average of whether or not the patient experienced complications. For non-HF hospitalisations, it was calculated as a weighted average of all costs except EB03H and EB03I. The number of recorded NHS attendances for each currency code was used as the weights in these calculations.

In order to align the ‘day costs’ with the tariff values reported in the NHS SRC, we have used a weighted average mean length of stay from all relevant currency codes, in combination with total costs, to get the relevant daily cost. The approach used was to divide total cost by mean length of stay. We acknowledge that this approach may be slightly unreflective of the true daily cost incurred in the NHS, but reiterate that it is not used in all base case analyses. Base case results are generated using the total tariff values and the expected number of events per month approach to costing.

A similar approach was used to derive the ‘day in hospital (leads)’ value, but using the total cost of a lead event as the numerator.

The cost of an outpatient visit was taken from the most recent version of the Personal Social Services Research Unit (PSSRU) review of unit costs of health and social care.

The relevant costs used in the model are reported in Table 66.

Table 66: Hospitalisation event costs

Item	Cost	Source
Day in hospital (HF)	£655.71	NHS SRC[140]
Day in hospital (non-HF)	£699.50	NHS SRC[58]
Day in hospital (leads)	£794.41	NHS SRC[140]
HF hospitalisation event	£2,295	NHS SRC[140]
Non-HF hospitalisation event	£2,448	NHS SRC[140]
Outpatient visits	£110.00	PSSRU 2010, Table 15.5[141]

5.5.3 Device system costs

5.5.3.1 Device average selling prices

The previous NICE appraisal of CRT used data from the now defunct Purchase and Supplies Agency (PASA) which referred to a cost year of 2004/2005. As the data are 8 years old we did not use this in the current model. A relevant HRG code exists for CRT-P implantation (EA07Z), which includes device acquisition, and procedure costs, but the existing HRG code for ICD implantation does not include device acquisition costs and does not distinguish between CRT-D and ICD implantation. It was therefore decided to source the most recent UK NHS specific average selling prices from the manufacturers via the Association of British Healthcare Industries (ABHI). These prices are an aggregate across all sponsors (manufacturers) of this submission for all ICD, CRT-P and CRT-D devices and leads (either as systems or devices/leads only) sold in the UK to the NHS. The data are the most accurate and up-to-date available and were elicited solely for the purpose of model parameterisation. The values provided by the ABHI are presented in Table 67 and refer to a cost year of 2011.

5.5.3.2 UK tariff prices (device implantation)

As noted above, a complete tariff exists for CRT-P implantation (HRG: E07Z - £8,281) which we have assumed, given the device acquisition cost, covers all relevant costs associated with the implant procedure. This tariff value is assumed to be sufficient to cover both procedural and acquisition costs. We know this is

the case, however, by virtue of payment based results (PbR) documentation which makes clear which devices are excluded from tariff – ICD and CRT-D.

Tariff values also exist for ICD non-purchase costs (HRG: EA12Z – £5,556) and lead revisions/ interventions not requiring a new device (HRG: EA39Z - £2,748). We have assumed that the ICD value is equally applicable to both ICD and CRT-D implants and that EA12Z will be used in all upgrade/ replacement operations. These values (ICD/CRT-D) have been used in combination with the relevant ASPs (as provided by the ABHI, see above) to generate all implant costs.

Table 67: ICD and CRT system costs

Item	Cost	Source
	System costs	
CRT-P whole system costs (device and leads)	£3,411	ABHI (data on file)
CRT-D whole system costs (device and leads)	£12,293	ABHI (data on file)
ICD whole system costs (device and leads)	£9,692	ABHI (data on file)
CRT Leads	£510	ABHI (data on file)
CRT-P pulse generator	£2,600	ABHI (data on file)
CRT-D pulse generator	£11,752	ABHI (data on file)
ICD generator	£9,149	ABHI (data on file)
	UK Tariff values	
CRT-P	£8,281	HRG E07Z
ICD non-purchase costs	£5,556	HRG EA12Z
Revisions not requiring new device	£2,748	HRG EA39Z

5.5.3.3 Additional costs incurred treating infection

As per Fox *et al.*[34] we have assumed that device related infection involves:

1) Explanation of the exiting device

2) Device reimplantation

3) Additional time in hospital

4) An additional outpatient visit

1), 3) and 4) are discussed above. In absence of data on excess bed day costs,

we have inflated the derived value in Fox *et al.*[34] to current equivalents using the HCHS Pay and Prices index (value used £3,139).

5.5.3.4 Values used in the model

The total cost values used in the model for all procedures are presented in Table 68.

Table 68: Device costs used in the model

Item	Cost	Components
Initial implant operation (ICD)	£15,248	ABHI system costs (incl. leads) and UK tariff EA12Z
Initial implant operation (CRT-P)	£8,281	UK Tariff E07Z
Initial implant operation (CRT-D)	£17,849	ABHI system costs (incl. leads) and UK tariff EA12Z
Replacement (ICD)*	£14,705	ABHI system costs (excl. leads) and UK tariff EA12Z
Replacement (CRT-P*)	£8,281	UK Tariff E07Z
Replacement (CRT-D)*	£17,308	ABHI System costs (excl. leads) and UK tariff EA12Z
Device related infection (ICD)	£18,964	See section 5.5.3.3
Device related infection (CRT-P)	£12,541	See section 5.5.3.3
Device related infection (CRT-D)	£21,568	See section 5.5.3.3
Battery replacement (ICD)	£12,004	ABHI generator costs (excl. leads) and UK tariff EA39Z[1]
Battery replacement (CRT-P)	£8,381	UK Tariff[1]
Battery replacement (CRT-D)	£14,672	ABHI generator costs (excl. leads) and UK tariff EA39Z[1]

* Values solely used in the calculation of device related infection costs; 1) Values adjusted to account for the small proportion who experience an infection related event.

5.6 Health related quality of life

The approach used to incorporate subgroup specific HRQoL into the model is described in detail in Section 4.4. When measured by improvements from baseline in MLWHF score, treatment related benefits exist for many years. Further, Cleland *et al.*[101] applied a mapping algorithm to the data from the CARE-HF study and showed that, when expressed as EQ-5D preference weights, there were significant benefits associated with both CRT-D and CRT-P at 18 months and study end ($p<0.001$ for both results).

However, expert clinical advice indicated that benefits would be unlikely to be

apparent forever in all patients. Hence, in contrast to the analyses undertaken by Buxton *et al.*[33] and Fox *et al.*[34], we have not assumed a constant lifetime 'treatment effect' for any of the three devices. Instead, we have assumed that the benefit observed at six months is maintained up to five years and thereafter begins to recede in a linear manner over the time period five to ten years. After ten years we have used the conservative assumption that, conditional on being alive, an individual with a CRT or ICD device will have no additional HRQoL benefit over an identical person receiving OPT.

5.7 Other parameters

The remaining parameters used in the model are presented in Table 69

Table 69: Remaining model parameters

Item	Value	Source
Discount rate (costs)	3.5% p.a.	NICE Reference Case[103]
Discount rate (benefits)	3.5% p.a.	NICE Reference Case[103]
Time Horizon	80 years	Effective lifetime horizon
Gender	Subgroup specific	
Starting age	Subgroup specific	

6 Results from the cost-effectiveness analysis

Results of the base case deterministic cost-effectiveness analysis are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology (24 subgroups for patients with LBBB and 24 subgroups for patients without). All individuals are assumed to have LVEF ≤35%. Ischemia did not substantively impact on cost-effectiveness; the results presented below are therefore applicable to both ischemic and non-ischemic patients.

In many cases, there is little difference between the best and second best options (when viewed in terms of incremental cost-effectiveness ratios), and there may be other issues that clinicians wish to take into account. Thus there seems to be a reasonable case for building clinical flexibility into the recommendations in those cases where the ICER differences between technologies are small and the uncertainty as to which is the preferred device is high.

NYHA class I/II

- QRS duration < 120ms: the ICERs are below £25,200 per QALY gained, when accounting for the number of patients in each group, ICD is still likely to be an acceptable use of resources.
- QRS duration 120-149ms: ICD is cost-effective (all ICERs below £17,100 per QALY gained). For CRT-D in patients with LBBB all ICERs are below £24,400 per QALY gained, meaning CRT-D is cost-effective.
- QRS duration ≥ 150ms, with or without LBBB: CRT-D is, overall, a cost-effective treatment.

NYHA class III

- QRS duration <120ms: ICD generates ICERs below £30,000 per QALY gained and is hence cost-effective

- QRS duration >150ms: CRT-P is cost-effective. Compared to CRT-P, CRT-D generates ICERs below £30,000 per QALY gained, and is cost-effective. ICD is either dominated or extended dominated.
- QRS duration 120-149ms: CRT-P is cost-effective. CRT-D generates ICERs between £23,900 and £27,400 per QALY gained relative to CRT-P, and provides significantly greater mortality reductions, so is likely to be an acceptable use of resources (i.e. cost-effective).

NYHA class IV

- QRS duration < 120ms: no comparative analysis was possible in this patient group.
- QRS duration ≥120ms: Compared to OPT, CRT-P represents value for money in NYHA class IV patients: all ICERs are close to or below £20,000 per QALY gained and hence cost-effective. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

Comparison with previous appraisals

- For CRT, the ICERs are nearly always lower than in the previous appraisal (except in NYHA class IV). In particular, the ICERs for CRT-D vs. CRT-P in NYHA class III are 30% to 50% lower than the accepted 2007 value.
- For ICD, the ICERs generated are similar to those in the previous appraisal generated assuming no EP testing in patients where ICD is recommended (NYHA class I/II, LVEF <35% and QRS <150ms).
- ICER improvements are likely to be due to lower real-terms device costs, increased device longevity, and better estimates of the impact of treatment on mortality and HRQoL.

Sensitivity analyses

- Sensitivity analyses were performed to explore alternative modelling assumptions and potential changes in the UK NHS. Most generated ICERs lower than, or similar to, the base case, confirming that the base case was indeed conservative.

- The base case assumed that treatment effects on mortality or HRQoL are not constant but diminish over time. When constant treatment effects for mortality and quality of life were explored, ICERs in all patient groups were lower than in the base case. In particular, the ICERs in patients who are NYHA class III with a QRS >150ms are reduced to no more than £24,600 regardless of LBBB status.
- When performing a “Real world scenario” for patients in NYHA class III (i.e. CRT-D vs. OPT), the highest ICER generated was £22,400 per QALY gained. The scenario is necessary due to the high risk of SCD and hence defibrillation. Defibrillation based therapy was cost-effective in this scenario.
- The scenario analysis surrounding the use of NYHA class as a treatment effect modifier resulted in the decisions for patients in NYHA I, II or IV being unchanged. The greatest impact of the alternative assumption was in NYHA class III, where the ICERs for CRT-D vs. CRT-P in patients regardless of LBBB status are now at most £26,700 per QALY gained. Hence CRT-D was cost-effective in this patient group in this scenario.

Recommended decision rules

- The aim was to generate simple decision rules to allow cardiologists to provide the most cost-effective intervention to a given patient. These recommendations make no distinction between ischemic and non-ischemic aetiology and can be summarised as follows:
- For patients without LBBB (LVEF <35%):
  - In NYHA class I/II, QRS < 150ms: ICD should be used. For QRS ≥150ms, the patient should be given CRT-D.
  - NYHA class III: where indicated, doctors should be allowed to use either CRT-D or CRT-P, with CRT-D the preferred device because of the incidence of SCD in this population. Patients with QRS < 120ms should be offered an ICD.
  - NYHA class IV: CRT-P is the treatment of choice (where indicated).

- For patients with LBBB (LVEF <35%):
  - NYHA class I, II or III: the treatment choice is CRT-D.
  - NYHA class IV: CRT-P device is the preferred option (where indicated).

6.1 Base case deterministic analysis

Results were generated in a two-stage process. In the first, both for patients with and without LBBB, cost and QALY estimates were derived for all relevant comparators in all 4,992 patient profiles (4 NYHA * 2 aetiology status (ischaemic/ non-ischaemic) *3 QRS categories * 4 LVEF categories* LBBB status (yes/no)* 2 gender groups * 13 age categories[6]).

In the second stage, these were collapsed to 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology. To provide results for each of these groups, it was necessary to aggregate over patients with different LVEFs, genders and ages. Results were aggregated over different LVEF values represented in the clinical trials as LVEF was not a strong predictor of cost-effectiveness across this range, and its inclusion would have increased the number of subgroups. Results were aggregated over age and gender categories as it is not expected that NICE would make different recommendations according to age or gender. The patient counts in the trial database for each LVEF-, age- and gender-defined patient profile were used as weights in the calculation of weighted average costs and QALYs for the 24 subgroups for each LBBB category.

The list of fully incremental base case results is presented in Table 70 for patients who do not have LBBB and in Table 71 for patients who do have LBBB. The deterministic CRT-D vs. ICD vs. OPT ICERs for patients with NYHA III are presented in Table 73 for both patient groups.

The labels in the columns titled ‘CE-Sequence’ detail the order in which interventions

[6] Age is described using 5- year bands starting at 35, with the top band being ‘greater than 85’

appear on the cost-effectiveness frontier, starting from the origin (least costly and least effective) and moving in a 'north east' direction to take in more effective and more costly options. The ICERs represent the relevant values for each indication along the frontier. Note that when fewer than four interventions are considered for a given subgroup, the values in both empty columns will be represented as “N/A”. Similarly, where no patients were identified for a given combination (e.g. with LBBB and QRS duration <120ms), values of N/A are reported in all boxes.

Table 70: Deterministic base case results (patients without LBBB)[7]

				C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	N	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	66	OPT	ICD	N/A	N/A	Referent	£24,304	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	11	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,619	N/A
I	Non-Ischemic	>=150ms	8	OPT	ICD	CRTD	N/A	Referent	£18,074	£1,080,057	N/A
I	Ischemic	<120ms	272	OPT	ICD	N/A	N/A	Referent	£24,016	N/A	N/A
I	Ischemic	>=120, <150 ms	216	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,234	N/A
I	Ischemic	>=150ms	106	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,086	N/A
II	Non-Ischemic	<120ms	710	OPT	ICD	N/A	N/A	Referent	£25,110	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	232	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,016	N/A
II	Non-Ischemic	>=150ms	141	OPT	ICD	CRTD	N/A	Referent	£20,312	£27,175	N/A
II	Ischemic	<120ms	788	OPT	ICD	N/A	N/A	Referent	£23,884	N/A	N/A
II	Ischemic	>=120, <150 ms	756	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,749	N/A
II	Ischemic	>=150ms	470	OPT	ICD	CRTD	N/A	Referent	£20,697	£22,777	N/A
III	Non-Ischemic	<120ms	255	OPT	ICD	N/A	N/A	Referent	£29,402	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	150	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£19,760	£27,336
III	Non-Ischemic	>=150ms	109	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,227	£24,350
III	Ischemic	<120ms	438	OPT	ICD	N/A	N/A	Referent	£26,923	N/A	N/A
III	Ischemic	>=120, <150 ms	426	OPT	CRTP	ICD	CRTD	Referent	£19,670	Ext Dominated	£24,796
III	Ischemic	>=150ms	192	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,392	£25,734
IV	Non-Ischemic	<120ms	5	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	12	OPT	CRTP	CRTD	N/A	Referent	£17,324	£30,624	N/A
IV	Non-Ischemic	>=150ms	9	OPT	CRTP	CRTD	N/A	Referent	£16,304	£33,901	N/A
IV	Ischemic	<120ms	42	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	52	OPT	CRTP	CRTD	N/A	Referent	£24,366	£43,500	N/A
IV	Ischemic	>=150ms	10	OPT	CRTP	CRTD	N/A	Referent	£18,065	£37,802	N/A

[7] Patients in NYHA I, non-ischaemic, QRS>150ms nearly all of one type – elderly males

Table 71: Deterministic base case results (patients with LBBB)

NYHA Class	Etiology	QRS Duration	N	C-E Sequence 1st	2nd	3rd	4th	ICERs 1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	21	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,021	N/A
I	Non-Ischemic	>=150ms	33	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,118	N/A
I	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	76	OPT	ICD	CRTD	N/A	Referent	£19,989	£24,343	N/A
I	Ischemic	>=150ms	165	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,335	N/A
II	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	385	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,608	N/A
II	Non-Ischemic	>=150ms	1,308	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,794	N/A
II	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	477	OPT	ICD	CRTD	N/A	Referent	£20,640	£21,277	N/A
II	Ischemic	>=150ms	982	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,479	N/A
III	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	189	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,550	£23,831
III	Non-Ischemic	>=150ms	775	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,798	£27,592
III	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	355	OPT	ICD	CRTP	CRTD	Referent	Dominated	£15,449	£25,540
III	Ischemic	>=150ms	773	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,408	£29,912
IV	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	22	OPT	CRTP	CRTD	N/A	Referent	£14,715	£31,920	N/A
IV	Non-Ischemic	>=150ms	81	OPT	CRTP	CRTD	N/A	Referent	£12,076	£35,660	N/A
IV	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	38	OPT	CRTP	CRTD	N/A	Referent	£22,340	£41,695	N/A
IV	Ischemic	>=150ms	97	OPT	CRTP	CRTD	N/A	Referent	£17,722	£46,445	N/A

Table 72: Deterministic base case results (NYHA III, CRT-D vs. OPT)

Pt. Group	**ΔCosts**	**ΔQALYs**	**ICER (£/QALY gained)**
Individuals without LBBB			
Non-Ischaemic, QRS between 120 and 149ms	£25,771	1.24	£20,850
Non-Ischaemic, QRS ≥150ms	£26,060	1.45	£17,968
Ischaemic, QRS between 120 and 149ms	£23,476	1.05	£22,412
Ischaemic, QRS ≥150ms	£24,730	1.27	£19,352
Individuals with LBBB			
Non-Ischaemic, QRS between 120 and 149ms	£27,019	1.56	£17,323
Non-Ischaemic, QRS ≥150ms	£27,514	1.79	£15,341
Ischaemic, QRS between 120 and 149ms	£24,073	1.20	£20,096
Ischaemic, QRS ≥150ms	£24,778	1.42	£17,514

Further to the additional NYHA III analyses presented in Table 72, as was noted in the introduction and in the definition of the decision problem, SCD remains the most

common form of death in this patient group. This would imply that, if CRT-D were unavailable, then clinicians would have a preference for ICD over CRT-P. This argument is supported by both the latest ESC and NICE guidelines.[4;5] Such a decision would be acceptable given the large overlap between guidance issued in TA95 and TA120. The relevant results presented in Table 70 and Table 71 were therefore regenerated with CRT-P removed as a treatment option (see Table 73).

Table 73: Deterministic base case results (NYHA III, CRT-D vs. ICD vs. OPT)

Pt. Group	ΔCosts (vs. OPT)		ΔQALYs (vs. OPT)		ICER (£/QALY gained)	
	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D
		Individuals without LBBB				
Non-Ischaemic, QRS between 120 and 149ms	£20,912	£25,771	1.06	1.24	£19,760[a]	£27,336[b]
Non-Ischaemic, QRS ≥150ms	£19,732	£26,060	0.76	1.45	Dominated	£17,968[a]
Ischaemic, QRS between 120 and 149ms	£19,006	£23,476	0.76	1.05	Dominated	£22,412[a]
Ischaemic, QRS ≥150ms	£19,113	£24,730	0.70	1.28	Dominated	£19,352[a]
		Individuals with LBBB				
Non-Ischaemic, QRS between 120 and 149ms	£20,101	£27,019	0.74	1.56	Dominated	£17,323[a]
Non-Ischaemic, QRS ≥150ms	£19,302	£27,514	0.50	1.79	Dominated	£15,341[a]
Ischaemic, QRS between 120 and 149ms	£18,650	£24073	0.64	1.20	Dominated	£20,096[a]
Ischaemic, QRS ≥150ms	£17,790	£24,778	0.41	1.42	Dominated	£17,514[a]

a) vs. OPT; b) vs. ICD;

6.1.1 Interpretation of base case results

Due to the varying number of treatment options assessed in each of the 48 patient groups, the results presented above require careful consideration and interpretation. In general, the discussion focuses on the most cost-effective option in each group for a given cost-effectiveness threshold. However, in many cases, there is little difference between the best and second best options (when viewed in terms of incremental cost-effectiveness ratios), and there may be other issues that clinicians wish to take into account. Thus there seems to be a reasonable case for building clinical flexibility into the recommendations in those cases where the ICER differences between technologies are small and the uncertainty as to which is the preferred device is high.

6.1.1.1 Patients with mild to moderate heart failure (NYHA class I/II)

QRS duration <120ms

Due to the definition of LBBB there are no patients with LBBB and QRS <120ms, and so all patients for whom CRT treatment was not indicated (QRS<120ms) are assumed to not have LBBB. The analysis performed was a pairwise comparison of ICD to OPT. The results were very similar in all patient groups (NYHA class I/II, ischaemic and non-ischaemic aetiology), with the ICER ranging from £23,884 to £25,110 per QALY gained.

There is good clinical evidence supporting the use of ICD devices in this patient group (see Section 3), and this is recognised both in previous NICE guidance and in international guidelines. Importantly, no difference in cost-effectiveness between ischaemic and non-ischaemic were observed.

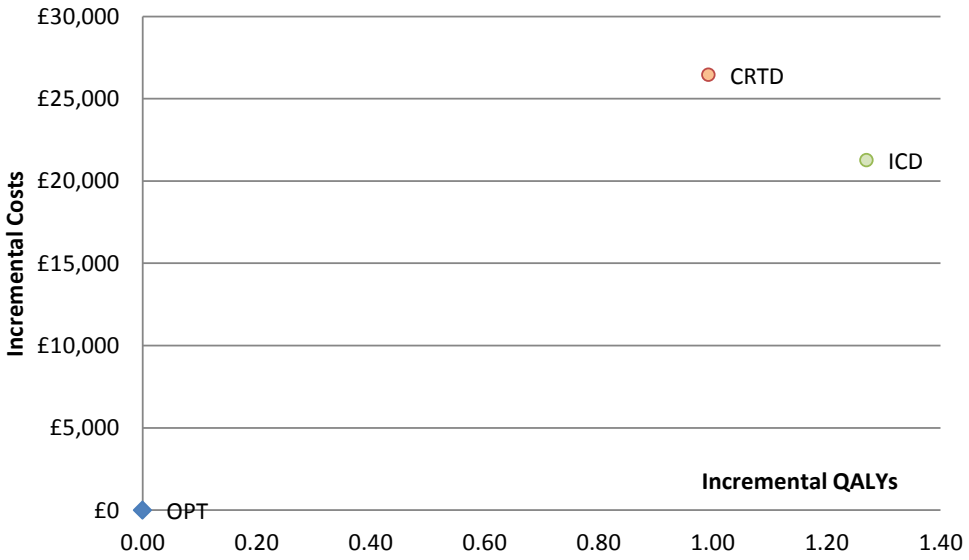
The ICERs are no more than £25,200 per QALY gained meaning that ICD therapy is still likely to represent an acceptable (cost-effective) use of health care resources in NYHA class I/II patients with or without ischaemia, with LVEF ≤35% and with QRS ≤ 120ms.

QRS duration 120ms to 149ms

In this group the interventions of interest are CRT-D, ICD and OPT, and the choice of intervention depends on LBBB status. The results from the network

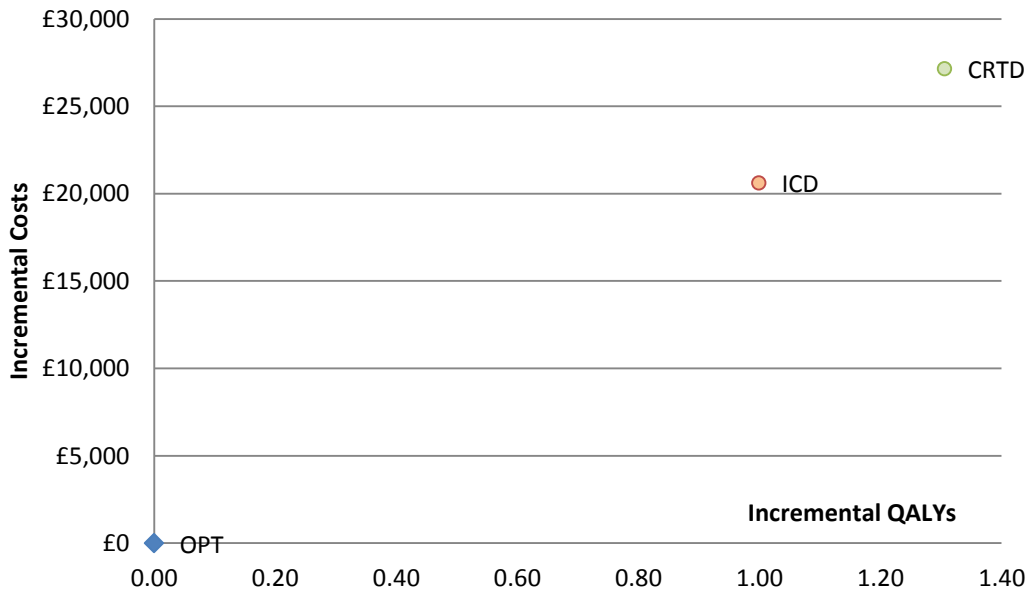
meta-analysis indicate that, in patients without LBBB, ICD and CRT-D are likely to be similar in terms of clinical efficacy with differences driven by parameter uncertainty and slight variations in patient mix (e.g. by age and gender). Thus, given the additional implant cost for CRT-D, this results in ICD being the dominant technology. The cost-effectiveness frontier for the patient group with the most patients in the trial database (NYHA class II and ischaemic aetiology, n=756) is presented in Figure 30. In all relevant patient groups the ICERs generated were below £20,000 per QALY gained (£16,234 to £17,016).

Figure 30: CE frontier (NYHA II, ischaemic aetiology, no LBBB)



LBBB was shown to be a strong treatment effect modifier in this patient group (pooled hazard ratio [redacted]), and the results from the network meta-analysis indicate that CRT-D is more clinically effective than ICD in patients with LBBB. The cost-effectiveness frontier for the most common patient profile in the trial database (NYHA class II, ischaemic aetiology, n=472) is presented in Figure 31. Similar frontiers are generated for all other relevant patient groups. In all relevant patient groups the ICERs generated were below £25,000 per QALY gained (£20,608 to £24,343).

Figure 31: CE frontier (NYHA II, ischaemic aetiology, LBBB)



ICD is a cost-effective treatment option in NYHA I/II patients with QRS duration 120-149ms and no LBBB and LVEF≤35%.

For CRT-D all ICERs are below £25,000 per QALY gained in LBBB patients (£20,608 to £24,343), meaning that CRT-D is a cost-effective intervention for NYHA class I/II patients with QRS duration 120-149ms with LBBB and LVEF ≤35%.

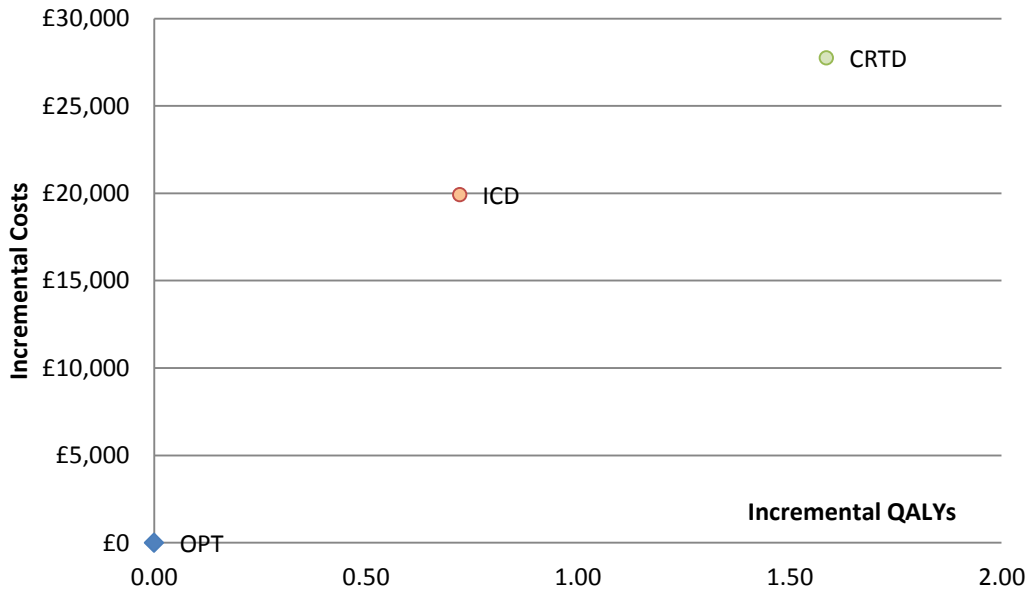
QRS duration at least 150ms

In patients with LBBB the argument presented above applies to those with QRS duration ≥ 150ms also, and the conclusions identical: CRT-D is a cost-effective intervention for this patient group (ICER range £17,335 to £18,118).

In patients without LBBB the interpretation is more subtle, as there were very small patient numbers in some profiles (in particular those with NYHA class I and non-ischaemic aetiology, n=8). The results generated for these groups are likely to be influenced by non-decision variables (age, gender, etc.), and so the results should be viewed 'in the round'. Across all four patient groups, and accounting for the fact that the great majority of patients had ischaemic aetiology, CRT-D emerges as a cost-effective treatment option (relevant ICERs ranging from £21,086 to £27,175 per QALY gained).

The cost-effectiveness plane for the most populated group (NYHA class II, ischaemic aetiology, n=470) is presented in Figure 32.

Figure 32: CE frontier (NYHA II, ischaemic aetiology, LBBB)



Overall, CRT-D is a cost-effective treatment for NYHA class I/II patients with QRS duration ≥ 150ms, with or without LBBB and with LVEF ≤35%.

6.1.1.2 Patients with moderate to severe heart failure (NYHA III)

QRS duration less than 120ms

The pairwise comparison of ICD to OPT results in cost-effectiveness ratios greater than £20,000 per QALY gained but lower than £30,000 per QALY gained (£26,923 to £29,402). The numbers generated were similar to those previously deemed acceptable by NICE in their positive recommendation for ICDs. They were predicated on the assumption used in our model that ICD confers no additional quality of life benefits over OPT, which may be unnecessarily pessimistic (see section 4.4.8).

QRS duration between 120 and 149ms

In contrast to the situation for NYHA I/II heart failure, four treatment options exist for this patient group. Across all patient groups, and regardless of LBBB status (with the exception of patients who are non-ischaemic and without LBBB), ICD

does not lie on the cost-effectiveness frontier, and is either dominated or extended dominated by other treatment options. Relative to the other treatment groups, the patient count in this outlier group is modest (n=150), so the results are again likely to have been driven by the distribution of non-decision variables. The cost-effectiveness planes for the largest non-LBBB and LBBB populations are presented in Figure 33 and Figure 34, respectively.

Figure 33: CE frontier (NYHA III, ischaemic aetiology, non-LBBB)

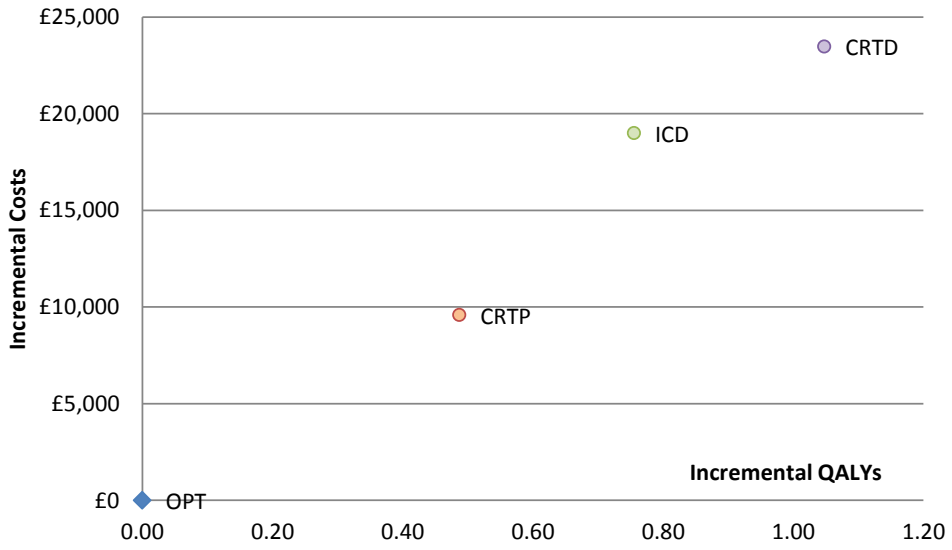
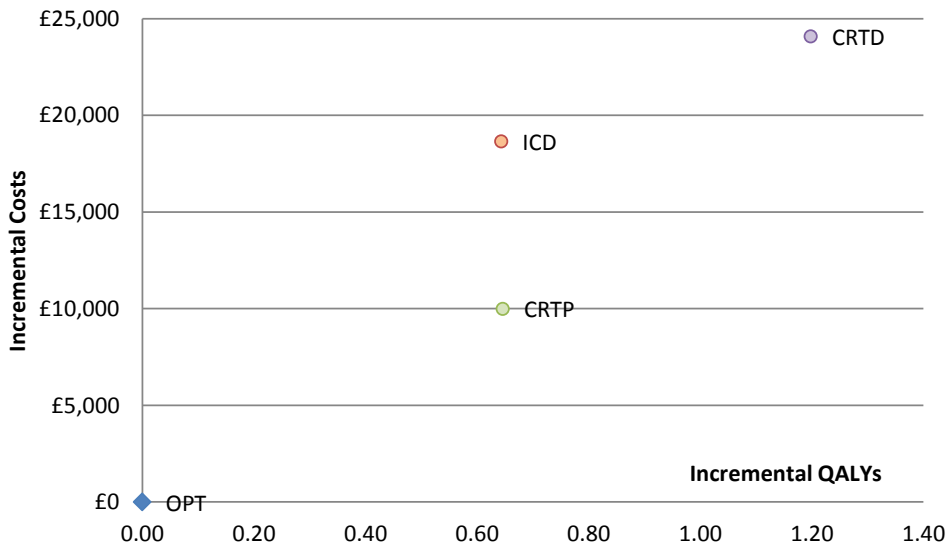


Figure 34: Cost-effectiveness frontier (NYHA III, ischaemic aetiology, with LBBB)



The ICERs generated for the pairwise comparison of CRT-P vs. OPT are similar to those generated by Fox *et al*.[34] in the previous NICE appraisal, and are all

below £20,000 per QALY gained. Hence, the current analysis confirms the previous findings. Of note, the ICERs generated in patients with LBBB are within £10,000-16,000 per QALY gained.

For the comparison of CRT-D to CRT-P, the ICERs generated are within the range of £23,831 to £27,336 per QALY gained). This is markedly lower than the value on which the previous positive recommendation was based (circa £40,000 per QALY gained).

The results of the NMA showed that CRT-D was significantly more effective than CRT-P in this patient group in terms of reducing all-cause mortality, and CRT-D is currently recommended for use in this group in all major clinical guidelines.[2;4]

The ICERs generated for the "real world" comparisons of CRT-D to OPT and CRT-D vs. ICD vs. OPT (i.e. as per current clinical practice) were all close to or below £20,000 per QALY gained. The need for this analysis was predicated on ICD being higher up in the clinical decision tree because of SCD being a major cause of mortality in this group, and also on the overlap between current ICD and CRT guidance, which means that clinicians are free to use any of the four treatment options.

All of the ICERs generated in this patient group are either close to, or markedly lower than, those deemed acceptable in the previous CRT appraisal.

CRT-P is a cost-effective treatment option in NYHA class III patients with QRS 120-149ms and LVEF ≤35%.

CRT-D generates ICERs slightly below £30,000 per QALY gained relative to CRT-P in this group, and provides significantly greater mortality reductions.

Overall, CRT-D in this patient group is likely to be a cost-effective use of the health care budget in the UK in NYHA class III patients with QRS 120-149ms and LVEF ≤35%.

QRS duration greater than 150ms

The overall picture in this group is similar to that in patients with a QRS duration

between 120 and 149ms. The only point of interest is that the ICERs for patients with LBBB are at the upper end of acceptable cost-effectiveness. This is driven by the marginally stronger interaction between LBBB and CRT-P efficacy compared to that between LBBB and CRT-D efficacy. This in turn leads to a small improvement in the efficacy of CRT-D compared to CRT-P in LBBB patients. However, as highlighted in section 1.1.6 SCD is still the main cause of mortality in this patient group meaning that there is a clinical need for CRT-D in this group.

Given the complexity of the model being fitted to the data, and in particular the large number of parameters being estimated, this difference is likely to be artificial and non-significant. We reiterate that CRT-D offered a significant reduction in all-cause mortality (see section 4.2) and so is a clinically efficacious treatment option in this group.

The result of this, as noted above, is a reduction in the ICER for CRT-P compared to OPT, and thus an increase in the ICER for CRT-D compared to CRT-P. The real world comparisons of CRT-D to ICD and/or OPT generated ICERs below £20,000 per QALY gained, which is supportive of CRT-D being cost-effective in this patient group.

Compared to OPT, CRT-P is a cost-effective treatment option in NYHA III patients with QRS >150ms and LVEF ≤35%.

Compared to CRT-P CRT-D generates ICERs close to £28,000 per QALY gained in this group. ICD is either dominated or extended dominated.

In the "real word scenario" the ICER generated for the comparison of CRT-D to OPT (ICD being dominated) is at most £20,096 per QALY gained.

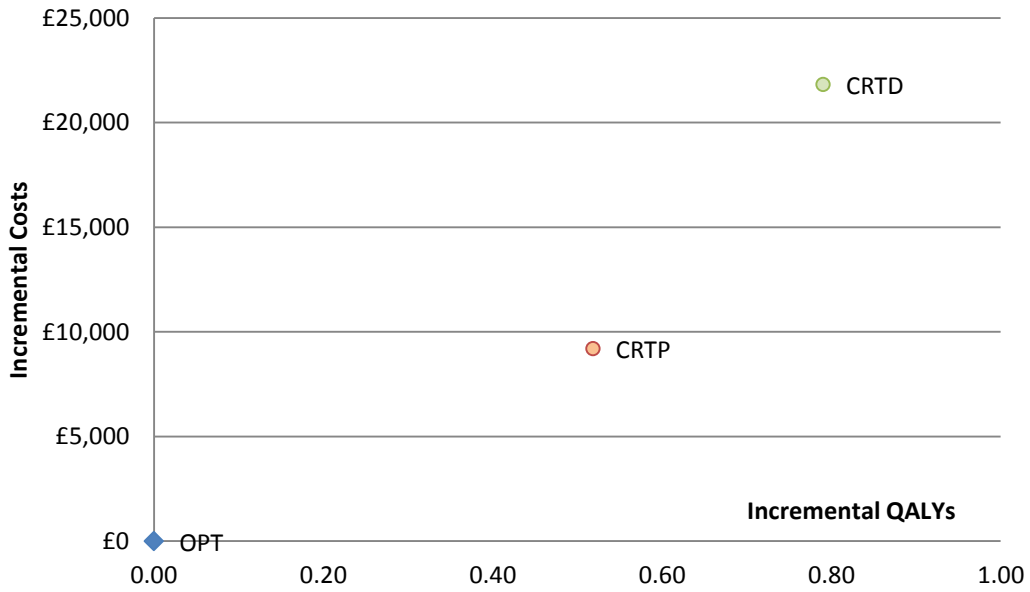
Overall, CRT treatment (both CRT-P and CRT-D) in this patient group are likely to be a cost-effective use of the health care budget in the UK in NYHA III patients with QRS >150ms and LVEF ≤35%.

6.1.1.3 Patients with severe heart failure (NYHA IV)

In general, compared to those discussed in previous results sections, all patient counts in the subgroups are modest with the largest group containing 97 individuals (QRS duration ≥150ms, ischaemic aetiology and LBBB). Hence, the

results are highly likely to be driven by small differences in patient level characteristics such as age, gender, LVEF etc. The cost-effectiveness plane for the largest patient group (LBBB, Ischaemic aetiology, QRS duration ≥150ms) is presented in Figure 35. When compared to OPT, CRT-P is a cost-effective treatment option with ICERs in the range £12,076 to 24,366 per QALY gained. When compared to CRT-P, CRT-D is unlikely to be cost-effective at conventional decision thresholds with ICERs in the range £30,624 to £46,445 per QALY gained.

Figure 35: CE frontier (NYHA IV, ischaemic aetiology, LBBB, QRS>150ms)



Compared to OPT, CRT-P represents good value for money in NYHA IV patients: all ICERs are close to or below £20,000 per QALY gained and so the treatment option is cost-effective. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

6.1.1.4 Comparison with results generated in previous appraisals

As part of the 2007 appraisal of CRT in patients with NYHA class III/IV heart failure, the model developed by Fox *et al*.[34] generated ICERs of approximately £16,700 per QALY gained for the comparison of CRT-P to OPT, and approximately £40,100 per QALY gained for CRT-D compared to CRT-P. The equivalent values generated in the current analysis are nearly always lower than

the previous values in all subgroups. In particular, the ICERs for CRT-D compared to CRT-P in NYHA class III patients are approximately 30% to 50% lower than the accepted 2007 value.

The ICERs that are higher than those used in previous guidance concern patients with NYHA IV heart failure. We believe that this is because the IPD based model allowed us to separate out NYHA class III and IV patients, and thus generate more nuanced results by more accurately identifying which devices are clinically effective in which patients and by enabling more accurate modelling of baseline risk.

The 2006 review of ICDs in primary prevention[33] generated a range of ICERs, with final values of between £33,000 and £46,000 per QALY gained if EP testing is not used. Assuming that EP testing is used to identify high risk patients, the ICERs ranged from £21,000 to £23,000 per QALY gained. EP testing is not included as a covariable in the current analysis, meaning that direct comparison with these historical results is not possible. The ICERs generated for ICD therapy in the nearest applicable groups (NYHA I/II, LVEF <35% and QRS <150ms) are similar to those generated previously when this test is used.

Given that EP testing was only conducted for all patients in one small ICD trial, it would not have been possible to produce evidence based estimates stratified according in this way. Perhaps more importantly, the ICERs presented in the previous appraisal referred to patients with previous MI only. The current analysis did not find substantive difference in the cost-effectiveness of ICD according to whether patients were ischemic or not, suggesting that separate recommendations for ischaemic and non-ischaemic patients are not required.

Thus, the ICERs from the current model are again markedly lower than were generated in the models developed during TA95 and TA120. The reasons for these improvements are likely to be a result of a combination of the following:

- Real term reduction in procedure costs (see section 1.7)
- Increases in device longevity compared to those used in previous models (see section 5.3.2 for current values)
- Better estimates of the impact of treatment on mortality (see section 4.2)

- Better understanding of the impact of treatment on HRQoL (see section 4.4)

Note that all three interventions received restricted positive recommendations in the previous appraisals on the basis of the above mentioned ICERs.

A final note concerns comparison of the results from this analysis with those from previous published cost-effectiveness studies, in particular those derived using information from SCD-HeFT and MADIT II.[130;142] Accepting the inherent problems in comparing the results of different models developed in different jurisdictions (hence reflecting different resource use patterns), different perspectives and different discount rates, the results from the two studies indicated that ischemic etiology is likely to impact on cost-effectiveness.

It is important to note that the discussion around the use of ischemic etiology surrounds its use as a decision variable. As can be seen from the results presented in Table 70 and Table 71, for a given LBBB/QRS/NYHA patient profile, the results vary by etiology. What is not clear is to what degree these results are driven by etiology as opposed to other variables (age, gender, BMI etc). it is also important to note that in all cases, the ICERs are below £30,000 per QALY gained for both groups suggesting that etiology should not be used to decide who does and does not get a given treatment.

6.2 Deterministic sensitivity analyses

6.2.1 Removal of treatment effect tapering (mortality)

The base case results were generated using the conservative assumptions that any treatment effects observed in the patient level data are not constant and diminish over time. This is in contrast to the assumptions used in both the *Fox et al.*[34] CRT model and the Buxton *et al.*[33] ICD model (with the latter accounting for the ageing process by way of multipliers for each decile above 60 years). We therefore explored the impact on cost-effectiveness of the use of constant treatment effects.

The results generated using this alternative modelling approach are presented in Table 74 and Table 75.

Table 74: Deterministic sensitivity analysis – constant mortality treatment effect (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£16,789	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£11,492	N/A
I	Non-Ischemic	>=150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,268	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£18,759	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,258	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,944	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£17,058	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,240	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£14,870	£20,863	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£18,587	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,792	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,513	£19,396	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,457	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£16,380	£58,164
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,583	£20,620
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,614	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,460	Ext Dominated	£23,391
III	Ischemic	>=150ms	OPT	CRTP	ICD	CRTD	Referent	£14,043	Ext Dominated	£23,297
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£17,201	£29,674	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£16,155	£32,552	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£24,316	£42,879	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,964	£36,827	N/A

Table 75: Deterministic sensitivity analysis – constant mortality treatment effect (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,840	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,725	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£16,756	£20,704	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,375	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,108	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,862	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£17,406	£17,951	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,548	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,751	£19,294
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,085	£21,682
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£15,174	Ext Dominated	£23,633
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,107	£26,979
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£14,453	£29,557	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£11,880	£32,921	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,302	£41,139	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,666	£45,471	N/A

Broadly speaking, and as would be expected, extending survival by assuming a constant treatment effect results in the ICERs in all patient groups being lower than in the base case. However, the resulting treatment decisions for patients with NYHA classes I, II or IV are unchanged. The greatest impact of the alternative assumption lies in patients who are NYHA class III, where the ICERs for patients with LBBB for the comparison of CRT-D to CRT-P are now at most £26,979 per QALY gained.

The exception to this pattern is in non-ischaemic NYHA III patients who have a QRS duration ≥120ms but no LBBB. This was the only NYHA III group for whom ICD was on the cost-effectiveness frontier in the base case, based on a modest number of patients in this subgroup (n=150). In this group, the aggregate treatment effect for ICD was greater than that for CRT-D ([redacted]) and hence, when this treatment effect is applied for the duration of the patient's lifetime, ICD becomes relatively more cost-effective. We note, however, that the difference in treatment effects is small and unlikely to be statistically significantly different.

The conclusion from this analysis is that the choice of the most cost-effective intervention(s) in this particular small patient group is very uncertain and, dependent on the assumptions made surrounding treatment efficacy, either CRT-D or ICD could be the preferred cost-effective option.

6.2.2 Removal of treatment effect tapering (HRQoL)

The results generated when all observed short/ medium term utility benefits are assumed to hold for all model cycles are presented in Table 76 and Table 77. In this scenario, ICD no longer appears on the cost-effectiveness frontier for patients who are NYHA class III, non-ischaemic, QRS duration between120ms and 149ms and have no LBBB. Further, all ICERs in patients with QRS duration ≥ 120ms are, on the whole, lower than in the base case, although the impact is modest. The derived results for patients who are NYHA class I/II with a QRS less than 120ms are very similar to those derived using the base case assumptions.

Table 76: Deterministic sensitivity analysis – constant HRQoL treatment effect (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,580	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,475	N/A
I	Non-Ischemic	>=150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,847	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,134	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,001	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,086	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,180	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,781	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,012	£28,961	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,995	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,500	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,393	£24,034	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£29,402	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£16,868	Ext Dominated	£18,982
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,558	£22,833
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,923	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£18,010	Ext Dominated	£23,535
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,060	£24,196
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£16,523	£29,338	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£15,486	£32,322	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£23,769	£42,278	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,388	£36,335	N/A

Table 77: Deterministic sensitivity analysis – constant HRQoL treatment effect (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,021	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,118	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,734	£25,637	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,335	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,608	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,794	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,315	£22,445	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,479	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,510	£22,085
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£8,611	£25,619
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,264	£24,177
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,687	£28,253
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£13,473	£30,040	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£11,415	£33,638	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£21,929	£40,622	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,399	£45,086	N/A

6.2.3 Removal of tapering of HRQoL and mortality treatment effect

The results generated using these combined assumptions are presented in Table 78 and Table 79.

Table 78: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£16,422	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£11,418	N/A
I	Non-Ischemic	>=150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,147	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£18,159	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,072	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,944	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£16,605	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,106	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£14,699	£21,949	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£17,986	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,593	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,263	£20,432	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,457	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£16,254	Ext Dominated	£16,388
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,992	£19,106
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,614	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£17,802	Ext Dominated	£22,067
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,722	£21,706
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£16,382	£28,295	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£15,316	£30,851	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£23,707	£41,543	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,266	£35,237	N/A

Table 79: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,840	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,725	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£16,549	£21,774	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,375	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,108	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,862	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£17,145	£18,878	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,548	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,863	£17,626
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£7,970	£19,810
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,985	£22,192
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,370	£25,215
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£13,244	£27,534	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£11,191	£30,712	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£21,882	£39,976	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,327	£43,955	N/A

Across all patient groups, the number of groups where CRT-D is likely to be recommended increased at a willingness to pay threshold of £30,000 per QALY gained. Of note, in patients who are NYHA III, ICD no longer appears on the cost-effectiveness frontier in any patient group. The ICER for the comparison of CRT-D to CRT-P in patients with NYHA III is at most £25,200 per QALY gained.

6.2.4 Use of alternative NYHA-based IPD results

As noted in Appendix 10, there is empirical evidence and a plausible clinical argument for CRT-D having a lower mortality treatment effect in patients with NYHA class IV compared to NYHA classes I/II/III. The results derived when the economic model is run using the estimated all-cause mortality treatment effects based on the grouping of NYHA class IV vs. NYHA class I-III patients are presented in Table 80 and Table 81.

This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups, especially NYHA class III, are lower than in the base case, with no meaningful CRT-D ICER being above £23,200 per QALY

gained.

Table 80: Deterministic sensitivity analysis –alternative all-cause mortality treatment effects (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,367	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,147	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,090	£1,095,407	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,243	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,795	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,874	£21,337	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,183	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,512	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£18,936	£27,571	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,109	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,276	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,270	£23,936	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£29,464	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£19,108	£21,754
III	Non-Ischemic	>=150ms	OPT	CRTP	ICD	CRTD	Referent	£13,661	Ext Dominated	£21,186
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,678	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	Ext Dominated	£21,363
III	Ischemic	>=150ms	OPT	CRTP	ICD	CRTD	Referent	£14,854	Ext Dominated	£22,737
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£17,337	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£15,974	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£24,152	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£17,570	N/A

Table 81: Deterministic sensitivity analysis – alternative all-cause mortality treatment effects (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,137	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,800	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,925	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,142	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,714	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,547	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,848	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,284	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£14,496	Ext Dominated	£17,158
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,186	£20,894
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£18,127	Ext Dominated	£18,787
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,834	£23,125
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£15,928	£129,051	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£12,142	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£24,113	£884,903	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£17,694	N/A

6.2.5 Increase in device longevity

The estimates of device lifetime are based on data from approximately 40,000 UK implants analysed by an independent research group (CCAD) and are higher than those used in previous models. This is in line with the hypothesis that ongoing technological improvements have resulted in devices lasting longer. In order to explore the impact of a continuation of this process we increased all mean device longevity by 10% by applying a scaling factor to the device specific lambda coefficient used to derive time dependent transition probabilities. The results of this analysis are presented in Table and Table 83.

Table 82: Deterministic sensitivity analysis – 10% increase in device longevity (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,855	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,313	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,747	£1,078,112	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,545	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,916	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,725	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,657	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,698	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,928	£27,095	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,419	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,421	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,292	£22,581	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£28,825	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£19,380	£27,099
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,029	£23,894
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,447	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,438	Ext Dominated	£24,301
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,201	£25,218
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£17,137	£30,042	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£16,124	£33,258	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£24,195	£42,839	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,891	£37,118	N/A

Table 83: Deterministic sensitivity analysis – 10% increase in device longevity (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,725	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,862	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,593	£24,147	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,044	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,306	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,536	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,233	£21,103	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,187	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,347	£23,422
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,647	£27,103
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£15,262	£25,030
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,269	£29,304
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£14,529	£31,341	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£11,933	£34,980	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,186	£41,050	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,599	£45,705	N/A

The impact on the ICERs was, overall, very modest. This is likely to be because of the very low replacement probabilities in the initial three to five year period, with the rate increasing rapidly thereafter. Slowing down the replacement rate in the population when notable proportions of the cohort are dead will have a small overall impact. We also ran the model using alternative parametric functions for the CRT-D replacement rates and the impact was again modest (results not shown). Hence, the model is insensitive to changes in this parameter.

The alternative scenario - a reduction in device longevity - was deemed highly implausible and so was not performed.

6.3 Results presented by LVEF category

All patients in the IPD dataset had LVEF of no greater than 35%, and are thus relatively uniform in this respect. In all regression analyses this parameter was viewed as categorical. Although LVEF below 40% is an important determinant of sudden cardiac death in clinical trials, this uniformity may have meant that its predictive effect was not apparent in the patient level data analysis of HRQoL or all-cause hospitalisation, and so it is not an important predictor of cost-effectiveness in our model. We have therefore not included results stratified by LVEF in the dossier, but the results can be identified in the economic model.

6.4 Probabilistic sensitivity analysis

The method we used to generate deterministic cost-effectiveness results has the advantage that it fully, and correctly, incorporates patient level heterogeneity into the analysis. The downside for this approach is that the model takes a long time to loop through all patient profiles. This computational expense means that a full PSA would take several months to execute. A probabilistic analysis for a given individual patient profile requires approximately five minutes.

We have, however, performed PSA simulations on individual patient profiles and compared these with the corresponding deterministic results to ensure that they are concurrent. These profiles were selected to reflect the baseline characteristics of the MADIT-CRT trial and are reported in Appendix 16.

6.5 Discussion of cost-effectiveness results

The motivating factor in this analysis was to generate simple, clinically appropriate decision rules which can be applied quickly in clinical practice and would allow cardiologists to provide the most cost-effective intervention to a given patient. We have worked closely with two highly respected UK cardiologists (Dr. Chris Plummer and Prof. Martin Cowie) to ensure that the methods, inputs, results and general direction of the project are aligned with current clinical thinking and practice.

To this end, where assumptions were made, we have endeavoured to be cautious in our choices:

- The effects of treatment on two key parameters (reduction in all-cause mortality and improvement in health related quality of life) were modelled to diminish over time.
- This approach was chosen as a conservative way of reflecting the uncertainty regarding long term device benefits.

In order to generate the pooled cost-effectiveness ratios we took into account the impact of gender, age, LVEF, QRS duration, aetiology, LBBB status and NYHA class. In the final analysis we did not present results stratified by age and gender since these were deemed to be ‘non-decision variables’. The precedent for this approach was set in the previous CRT appraisal where, despite evidence presented to the Appraisal Committee that cost-effectiveness depended on the starting age used in the model, this was not included in the final guidance.

Of the other variables, our analysis showed that the aetiology of heart failure (ischaemic or non-ischaemic) did not have a significant impact on cost-effectiveness: the results generated for each group, when differences in patient counts were accounted for, were very similar. The exploratory analysis undertaken whereby results were stratified by LVEF category (not presented) showed that this variable had little impact. The discussion henceforth does not distinguish between LVEF categories, and all results are predicated on having a LVEF of at most 35% (the inclusion criteria in the trials from which our data were taken).

The results from the economic model should also be viewed in the context of the

results from the network meta-analysis, and in particular the summaries of treatment efficacy presented in section 4.5.5. Of note, however, is the fact that the cost-effectiveness results represent pooled results across males and females as well as different age groups. The results also combine quantity and quality of life in each of the pooled groups meaning that the results from each of the subgroups cannot be directly compared. Nonetheless, the results from the clinical efficacy analysis identified increased efficacy for CRT-D and reduced efficacy for ICD as QRS duration increased. The analysis also indicated CRT-D having greater efficacy in patients with LBBB as opposed to those without.

6.5.1 Summary of findings

A summary of the most cost-effective interventions with an ICER below £30,000 per QALY gained is presented for all key analyses in Table 84 (for patients without LBBB) and Table 85 (for patients with LBBB). The numbers given are the ICERs, with the technology that generated the ICER in brackets. The treatment choices presented in these tables are in line with the key conclusions from the analysis of clinical efficacy presented in detail in section 4.5.5 and summarised above.

In generating these tables, we have used the results for individuals with ischaemic aetiology, but the results for patients with non-ischaemic aetiology were very similar. As the additional deterministic sensitivity analyses reported in Appendix 15 only had modest impacts on the ICERs, we have excluded them from these tables.

The majority of the sensitivity analyses performed to explore alternative modelling assumptions and future changes to the UK health care sector produced ICERs results lower than, or similar to, those generated in the base case, confirming that the base case was indeed conservative.

Table 84: Summary of most cost-effective ICERs across all analyses (ischaemic individuals without LBBB)

Subgroup	Base Case	Constant mortality treatment effect	Constant HRQoL treatment effect	Constant mortality and HRQoL treatment effects	NYHA as treatment effect modifier	Mean device longevity increased by 10%
NYHA I , QRS <120ms	£24,016 (ICD)	£18,759 (ICD)	£23,134 (ICD)	£18,159 (ICD)	£24,243 (ICD)	£23,545 (ICD)
NYHA II, QRS <120ms	£23,884 (ICD)	£18,587 (ICD)	£22,995 (ICD)	£17,986 (ICD)	£24,109 (ICD)	£23,419 (ICD)
NYHA III, QRS <120ms	£26,923 (ICD)	£24,614 (ICD)	£26,923 (ICD)	£24,614 (ICD)	£26,678 (ICD)	£26,447 (ICD)
NYHA IV, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA I, QRS ≥120ms, <150ms	£16,234 (ICD)	£13,258 (ICD)	£16,001 (ICD)	£13,072 (ICD)	£15,795 (ICD)	£15,916 (ICD)
NYHA II, QRS ≥120ms, <150ms	£16,749 (ICD)	£13,792 (ICD)	£16,500 (ICD)	£13,593 (ICD)	£16,276 (ICD)	£16,421 (ICD)
NYHA III, QRS ≥120ms, <150ms	£24,796 (CRT-D)	£23,391 (CRT-D)	£23,535 (CRT-D)	£22,067 (CRT-D)	£21,363 (CRT-D)	£24,301 (CRT-D)
NYHA IV, QRS ≥120ms, <150ms	£24,336 (CRT-P)	£24,316 (CRT-P)	£23,769 (CRT-P)	£23,707 (CRT-P)	£24,152 (CRT-P)	£24,195 (CRT-P)
NYHA I, QRS ≥150ms	£21,086 (CRT-D)	£17,944 (CRT-D)	£21,086 (CRT-D)	£17,944 (CRT-D)	£21,337 (CRT-D)	£20,725 (CRT-D)
NYHA II, QRS ≥150ms	£22,777 (CRT-D)	£19,396 (CRT-D)	£24,034 (CRT-D)	£20,432 (CRT-D)	£23,936 (CRT-D)	£22,581 (CRT-D)
NYHA III, QRS ≥150ms	£25,734 (CRT-D)	£23,297 (CRT-D)	£24,196 (CRT-D)	£21,706 (CRT-D)	£22,737 (CRT-D)	£25,218 (CRT-D)
NYHA IV, QRS ≥150ms	£18,065 (CRT-P)	£17,964 (CRT-P)	£17,388 (CRT-P)	£17,266 (CRT-P)	£17,570 (CRT-P)	£17,891 (CRT-P)

Table 85: Summary of most cost-effective ICERs across all analyses (ischaemic individuals with LBBB)

Subgroup	Base Case	Constant mortality treatment effect	Constant HRQoL treatment effect	Constant mortality and HRQoL treatment effects	NYHA as treatment effect modifier	Mean device longevity increased by 10%
NYHA I , QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA II, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA III, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA IV, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA I, QRS ≥120ms, <150ms	£24,343 (CRT-D)	£20,704 (CRT-D)	£25,637 (CRT-D)	£21,774 (CRT-D)	£18,925 (CRT-D)	£24,147 (CRT-D)
NYHA II, QRS ≥120ms, <150ms	£21,277 (CRT-D)	£17,951 (CRT-D)	£22,445 (CRT-D)	£18,878 (CRT-D)	£18,848 (CRT-D)	£21,103 (CRT-D)
NYHA III, QRS ≥120ms, <150ms	£25,540 (CRT-D)	£23,633 (CRT-D)	£24,177 (CRT-D)	£22,192 (CRT-D)	£18,787 (CRT-D)	£25,030 (CRT-D)
NYHA IV, QRS ≥120ms, <150ms	£22,340 (CRT-P)	£22,302 (CRT-P)	£21,929 (CRT-P)	£21,882 (CRT-P)	£24,113 (CRT-P)	£22,186 (CRT-P)
NYHA I, QRS ≥150ms	£17,335 (CRT-D)	£14,375 (CRT-D)	£17,335 (CRT-D)	£14,375 (CRT-D)	£16,142 (CRT-D)	£17,044 (CRT-D)
NYHA II, QRS ≥150ms	£17,479 (CRT-D)	£14,548 (CRT-D)	£17,479 (CRT-D)	£14,548 (CRT-D)	£16,284 (CRT-D)	£17,187 (CRT-D)
NYHA III, QRS ≥150ms	£29,912 (CRT-D)	£26,979 (CRT-D)	£28,253 (CRT-D)	£25,215 (CRT-D)	£23,125 (CRT-D)	£29,304 (CRT-D)
NYHA IV, QRS ≥150ms	£17,722 (CRT-P)	£17,666 (CRT-P)	£17,399 (CRT-P)	£17,327 (CRT-P)	£17,694 (CRT-P)	£17,599 (CRT-P)

6.5.2 Cost-effective interventions by patient group

A summary of the choice of cost-effective interventions in each patient group is presented in Table 86.

*Table 86: Summary of cost-effectiveness recommendations arising from our analysis**

NYHA	QRS <120ms	QRS 120-150ms	QRS >150ms
I	ICD	ICD (No LBBB) CRT-D (with LBBB)	CRT-D (Both LBBB groups)
II	ICD	ICD (No LBBB) CRT-D (with LBBB)	CRT-D (Both LBBB groups)
III	ICD	CRT-D/ CRT-P (both LBBB groups)	CRT-D/ CRT-P (both LBBB groups)
IV	OPT	CRT-P (Both LBBB groups)	CRT-P (Both LBBB groups)

* all individuals also have LVEF<35% and no myocardial infarction within the past 4 weeks; the results apply to both ischaemic and non-ischaemic patients.

6.5.2.1 Patients without LBBB (LVEF <35%)

- **In NYHA class I/II patients without LBBB who have a QRS duration of less than 150ms, ICD should be used. When the QRS duration is ≥150ms the patient should be given CRT-D.**
- **For NYHA class III patients, where indicated, doctors should be allowed to use either a CRT-D or a CRT-P device since both are clinically- and cost-effective interventions, with CRT-D being the preferred device due to the incidence of SCD in this population. NYHA class III patients with QRS duration less than 120ms should be offered an ICD.**
- **CRT-P is the treatment of choice in patients who are NYHA class IV and QRS duration of at least 120ms.**

6.5.2.2 Patients with LBBB (LVEF <35%)

For patients with LBBB the key decision variable is NYHA class:

- **For patients in NYHA class I, II or III the treatment of choice is CRT-D. CRT-P is also to be a treatment option for patients who are in NYHA class III**
- **For those in NYHA IV a CRT-P device is the preferred option.**

It is interesting to note that clinical opinion provided during the development of the model indicates that in both LBBB groups, the findings highlighted above are the choices being made in routine clinical practice. Guidance reflecting the findings we present would be in line with the expectations of the clinical community, meaning that implementation would likely be high and budgetary impact low, given that this cost is already likely to be borne by the NHS under current financing.

6.5.2.3 Uncertainties and the need for clinical flexibility

For a number of the patient groups, the ICERs for several interventions compared to the previous element of the frontier are very similar. This means that the cost-effectiveness frontier is very flat, and plausible small changes to assumptions can result in interventions switching from being cost-effective to dominated or extended dominated. There is thus a high level of uncertainty in these patient groups regarding the choice of the ‘best’ device.

While exploratory, the probabilistic sensitivity analysis (PSA) results presented in Appendix 16 also indicate that the impact of parameter uncertainty is likely to be high. This is likely to be driven by the focus in our IPD analysis on fully capturing patient heterogeneity: by introducing a series of interaction effects, this necessarily reduces treatment effect precision. Our analysis does not suggest uncertainty regarding the overall efficacy of the devices, which is clearly demonstrated in the unadjusted network meta-analysis (see Section 4.2).

Finally, it is important to note that the cost-effectiveness results and the clinical effectiveness evidence concur, and there is no reason to treat ischaemic and non-ischaemic cardiomyopathy differently in terms of device therapy.

Hence, we recommend that guidance should be flexible, to allow clinicians to select the most appropriate device for a given patient in cases where the ICERs for two or more interventions are sufficiently similar.

6.5.2.4 Additional considerations

Despite having patient level data on over 12,000 individuals, it was not possible to answer all clinically relevant questions. The available evidence on these is presented below

- Atrial fibrillation: As noted in Section 2, these patients were excluded from most of the RCTs, and the resulting lack of data meant that we could not distinguish between patients with and without AF in our analysis. Only one of the trials in the IPD database included patients with permanent AF at baseline (RAFT[80]). Results from RAFT showed no statistically significant difference between patients with permanent atrial fibrillation or flutter vs. those whom were in sinus rhythm or were atrially paced (p-value for interaction = 0.14 for primary endpoint of death or hospitalisation for heart failure). However the power of this analysis to detect any interaction effect is likely to have been limited by the number of patients in the permanent atrial fibrillation or flutter subgroup (n=229).
- Previous NICE guidance for ICD was predicated for some patients on patients having non-sustained VT on Holter monitoring and inducible VT on EP testing for patients with QRS duration <120ms or LVEF between 30-35%. Non-sustained VT on ECG was only collected in three of the smaller ICD trials (MUSTT, DEFINITE and MADIT) and EP testing in only one small ICD trial (MADIT). It would therefore be difficult to make evidence based statements stratified according to these tests
- Previous NICE guidance for CRT was predicated on the presence of mechanical dyssynchrony for patients with QRS 120-149ms. This appears to be based on the inclusion criteria for CARE-HF (the only study in which these data were collected). However, analysis of the IPD from CARE-HF shows that only [redacted] of patients in CARE-HF had QRS in the range 120-149ms. This

suggests that the favourable results in CARE-HF were driven by the wider QRS of patients in this trial (which was found to modify CRT efficacy in our analysis), rather than by the mechanical dyssynchrony criteria.

Also, the data from the clinical trials did not include the rarer ICD indications – hypertrophic cardiomyopathy, arrytthmogenic right ventricular dysplasia, long QT Syndrome, etc., and so we were not able to assess which interventions should be used in these groups. Smaller trials and registries remain the best available information source on which to base treatment decisions in these patient groups.

7 Financial implications to the NHS and other parties

- The recommendations from the ABHI analysis presented in section 6.5.2 would lead to a widening of the eligibility criteria for an ICD or CRT device and consequently an increase in implant rates, but growth in uptake is likely to be gradual.
- Growth in implant rates should be viewed in the context that current rates are still below the minimum levels suggested under current guidance and the implant rates in other developed countries in Europe and North America.
- It is difficult to predict future implant rates for each device type because of unknowns relating to switching rates between types (e.g. ICD to CRT), and incomplete epidemiological data on the numbers of patients in each eligible group. It is therefore not feasible to present a full budget impact analysis.
- We present estimates of the annual cost of treatment under current and alternative scenarios. These represent the costs above and beyond those that would be incurred if patients remained on medical management alone.
- Depending on the choice of scenario and year of interest, the additional annual expenditure incurred by the NHS ranges from £41.6 million to £230.2 million.
- The majority of interventions were shown to be cost-effective in the groups where they are indicated. Hence, the cost of services displaced through the use of these technologies would be expected to be higher than the costs incurred (for example, hospitalisation rates would be reduced).

7.1 Introduction

The conclusions from the ABHI model described in section 6.5.2 would lead to an increase in implant rates, with the associated financial costs. However, experience with related technologies suggests that growth in implant rates is likely to be gradual rather than sudden. For example, uptake of pacemakers in England was still only 528 per million in 2010 – well below Heart Rhythm UK's national target of 700 per million, even though access to these devices is relatively unrestricted.[21] Furthermore, removal of the requirements for Holter monitoring, electrophysiology testing and echocardiography for dyssynchrony would mean that an increased implantation rate would be simpler and cheaper to implement than under the current recommendations.

Most importantly, the devices under consideration bring survival and symptomatic/quality of life benefits to patients in the proposed widened indications. We have shown them to be cost-effective. As current implantation rates do not yet reach even previously suggested minimum levels, we would argue that an increase in implantation rates to include the patients under discussion is clinically and humanistically desirable in terms of QALYs gained, and the cost of these benefits would not exceed willingness to pay thresholds.

The implications for switching rates (ICD to CRT, CRT-P to CRT-D, etc.) of such revised guidance are unknown. It is also unknown how many patients would be included who are currently treated with ICD but who technically lie outside of existing guidance (i.e. those with no history of MI). Furthermore, epidemiological data on the number of patients in each group is not as comprehensive as would ideally be required for a full budget impact analysis. Because of these unknowns, any attempt to predict revised implant rates is speculative. The following impact assessment is presented to assist in providing as credible an estimate as possible of the financial implications to the NHS, using the available evidence both from this submission and from real world NHS clinical practice. We will present 'current' and 'alternative' scenarios in terms of the split between CRT-P and CRT-D within CRT implant rates, and different projected increases in ICD implantation rates.

7.2 Implant rates arising from previous appraisals

The financial implications sections of previous independent academic submissions were brief and did not contain any replicable methodologies. As part of the previous review of ICDs, an estimated annual implant rate of 100 per million population was generated for budget impact purposes. This rate represented a doubling of the value derived during TA11.[33] The review associated with that appraisal quotes an audit of clinical records undertaken at an English tertiary hospital to determine the eligibility of patients for ICDs against the NICE guidance of the time. This study reported under-provision of ICD therapy in the UK, and found that the number of patients eligible for ICDs exceeded that predicted. The annual incidence of patients fulfilling national criteria was about 150 per million, with an additional 'prevalence' pool of about 41 per million. The authors calculated that applying the MADIT II criteria to determine eligibility for ICD would increase the number to 504 per million (new cases) and 311 per million (prevalent cases) per year. Thus, the targets for ICD arising from previous NICE appraisals potentially underestimate the size of the target population by a factor of between 10 and 25.

There was no implant rate estimate in the previous CRT appraisal. Subsequent extrapolation from prevalence studies estimated a required CRT implantation rate of 130/million/year, and this has been adopted as a target by the UK National Audit of Cardiac Rhythm Management Devices.[21]

We have estimated the financial implications of our proposed guidance in terms of changes to implant rates.

7.3 Input values for current budget impact assessment

7.3.1 UK population estimates

The UK National Statistics Database[143] was examined to derive the latest population size estimate for England and Wales. To this value, we have applied an assumed 1% annual growth rate to derive population estimates for the years 2012-2016 inclusive. The values used in the model are presented in Table 87.

Table 87: England and Wales population estimates (in millions) 2012-2016

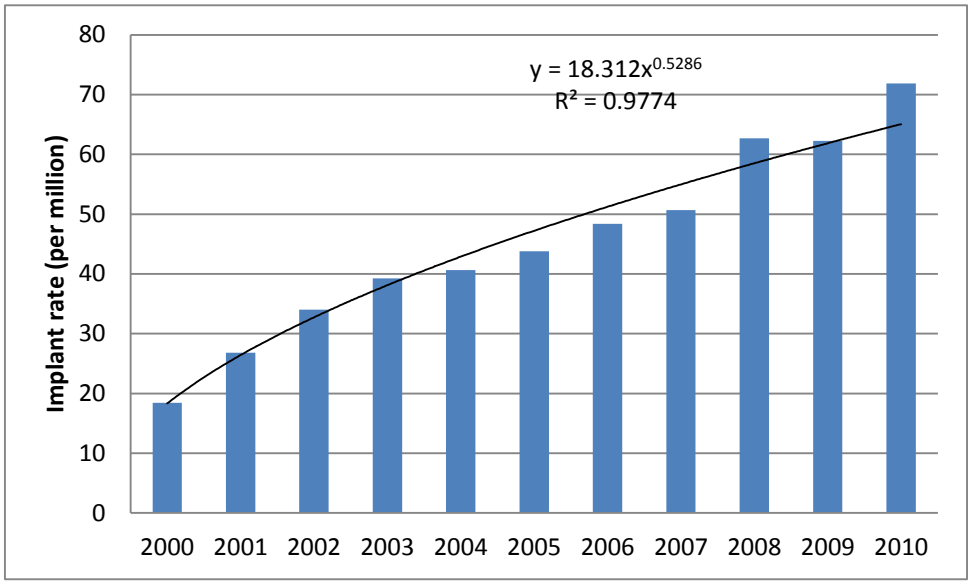
	2012	2013	2014	2015	2016
Value used	63.758	64.271	64.776	65.271	65.755

7.3.2 Implant rates used in 'current scenario'

ICDs

The principal document we have drawn on is the latest National Device Survey by the CCAD research group, which contained implant rates for England and Wales from years 2000 to 2010 inclusive.[21] A plot of the weighted average of the reported figures for England and Wales is presented in Figure 36, with a trend line.

Figure 36: England and Wales annual ICD implant rates (Data taken from Cunningham et al.)



The trend shows a slowing down in the change in implant rate over time. It is also noteworthy that the observed implant rates in all years are below the previous estimates derived by the independent evidence review group (discussed in Section 7.2 above). The fitted line was used to derive estimates of the expected ICD implant rates for 2012-2016 inclusive. The trend line is suggestive of a plateau effect being observed. Such an effect would arise due to patients who would historically have been offered an ICD device now being offered a CRT-D. This observation is further evidence that the conclusions of this submission are

aligned with routine clinical practice.

The predicted ICD implant rates used in the model, along with estimates of the number of implant procedures, are presented in Table 88.

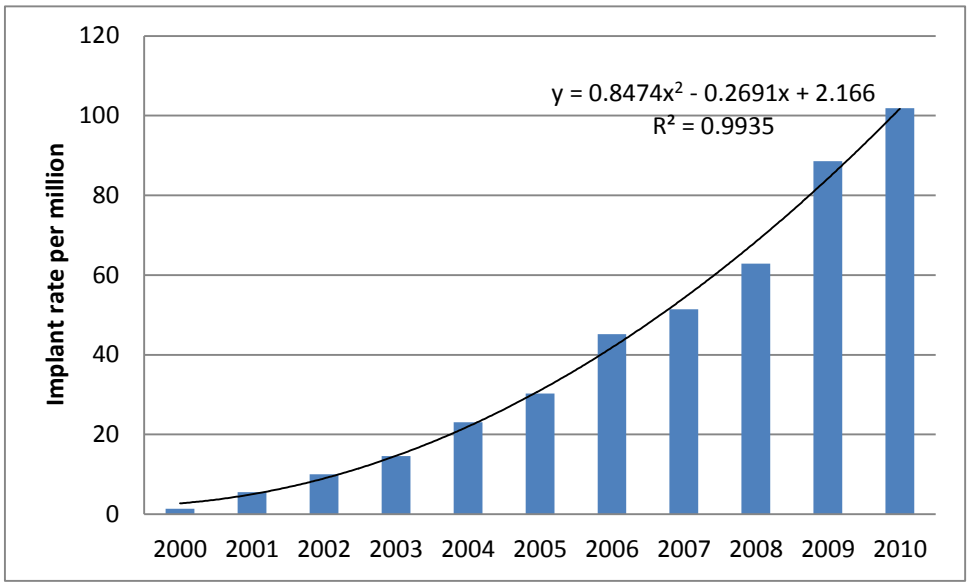
Table 88: Projected ICD implant rates (per million) and procedure counts

	2012	2013	2014	2015	2016
Implant rates	71.1	73.9	76.6	79.3	81.9
Procedure count	4,553	4,750	4,962	5,176	5,385

CRT

Cunningham *et al.*[21] also report equivalent data for CRT implant rates; the corresponding plot of the weighted average values for England and Wales is presented in Figure 37 (with the best fitting trend line). In this case the trend is increasing.

Figure 37: England and Wales annual CRT implant rates (Data taken from Cunningham et al.)



Within the CCAD report it is not possible to assess the historical CRT-D/CRT-P case mix for new implants. Relevant information can, however, be derived from the UK Health Episode Statistics (HES) database for years 2009/10 and 2010/11.[144] The relevant data are presented in Table 89. The proportion of patients who were given a CRT-D device in 2010/11 is in line with device use splits for the UK and Western Europe.[145] The rapid growth in CRT-D usage in

recent years is a further indication of a potential switch from ICD to CRT-D usage.

Table 89: New implant counts (CRT-P and CRT-P) reproduced from the HES database

Code	Description	2009/10	2010/11
E07Z	Pace 3 - Biventricular and all congenital pacemaker Procedures - Resynchronisation Therapy	1,882	1,952
K59.6	Implantation of cardioverter defibrillator using three electrode leads	1,198	1,920
K61.7	Implantation of biventricular cardiac pacemaker system	61	71
	TOTAL: CRT-P (E07Z)	1,882	1,952
	TOTAL: CRT-D (K59.6, K61.7)	1260	1,991
	Proportion of implants CRT-D	40.1%	50.5%

In projecting forwards, we have therefore used the assumption that 50.5% of CRT patients receive a CRT-D and 49.5% receive a CRT-P device. We have also included a notional 'braking coefficient' on the projected implant rates of 2.5% per year to simulate a future plateau effect for CRT usage. The derived rates and the procedure counts are presented in Table 90.

Table 90: Projected CRT implant rates (per million) and procedure counts

	2012	2013	2014	2015	2016
Implant rates	141.9[a]	161.4[b]	179.5[c]	199.1[d]	219.1[e]
Procedure count (CRT-D)	4,569	5,539	5,872	6,563	7,275
Procedure count (CRT-P)	4,478	5,135	5,756	6,433	7,131

a) Value excluding braking effect 141.9 per million; **b)** Value excluding breaking effect 164.5 per million; **c)** Value excluding breaking effect188.8 per million; **d)** Value excluding breaking effect 214.8 per million; **e)** Value excluding breaking effect 242.5 per million

7.3.3 Implant rates used in 'alternative' scenarios

A large proportion of patients who would become eligible for a CRT-D under the potential new guidance lie within the current eligibility criteria for an ICD. Given the small difference in implant costs, the budget impact of the recommendations of this submission could be limited if CRT-D is given mainly to patients previously given ICD. However, it is likely that CRT-D use would increase at the expense of

ICD implant rates, because of the additional symptomatic benefits that CRT-D offers to patients with HF.

As an alternative to the 'current' scenario described above, we have assumed that as a result of the new guidance, CRT usage will continue on its current trajectory (see Table 91), but the CRT-D/CRT-P split will be 75%/25%. To reflect the greater use of ICDs in NYHA I/II patients we have assumed a range of multipliers to the projected current ICD implant rates (25% increase, 50% increase, 100% increase, 200% increase).

As the UK has failed to fully implement previous NICE guidance and is already lagging behind the value previously used to estimate budget impact in TA95 of 100 implant per million, the base value for these projections could be considered unduly low. The derived estimates are to be viewed as minimum bounds and not as targets to be regarded as ceiling rates.

The annual ICD implant rates used in the alternative scenarios are presented in Table 91.

Table 91: Implant rates (per million) used in all alternative scenarios

	2012	2013	2014	2015	2016
CRT (all scenarios)	141.9	161.4	179.5	199.1	219.1
- Of which CRT-P	35.5	40.4	44.9	49.8	54.8
- Of which CRT-D	106.4	121.0	134.6	149.3	164.3
ICD (scenario 1: 25% increase on current projections)	88.9	92.4	95.8	99.1	102.4
ICD (scenario 2: 50% increase on current projections)	106.7	110.9	114.9	119.0	122.9
ICD (scenario 3: 100% increase on current projections)	142.4	147.8	153.2	158.6	163.8
ICD (scenario 4: 200% increase on current projections)	213.3	221.1	229.8	237.9	245.7

7.3.4 Annual cost of treatment

An estimate of the 5 year (undiscounted) cost of treatment with the new intervention compared with the old one is a fundamental element of any financial impact analysis. In this instance, the relevant costs are all those that would be incurred *above and beyond what would be incurred if patients had remained on medical management*. Treatment and subgroup specific model outputs for the 48

patient groups discussed in Section 6.1 were weighted by the proportion of patients in each group, to generate the values for annual cost of treatment, conditional on being alive, presented in Table 92. Note that in patient groups where a given intervention is contraindicated (e.g. ICD in NYHA IV), these patients have not been included in the weighted average calculations. The increase in annual values is due to reoperations. The rates of growth for each device type are based on the parametric functions described in section 5.3.2. Hence, because CRT-D devices are expected to fail quicker than ICD or CRT-P the values will rise at a greater rate.

Table 92: Annual cost of treatment estimates used in the financial impact assessment

	2012	2013	2014	2015	2016
ICD	£15,710	£230	£441	£611	£735
CRT-P	£8,294	£80	£86	£88	£88
CRT-D	£19,042	£468	£852	£1,142	£1,327

7.3.5 Survival estimates

It is essential to know what proportions of patients who get each treatment survive to subsequent years. Weighted average model outputs were again used in the analysis: the values are presented in Table 93. Note that due to differences in device usage across NYHA classes (and in particular the assumption that CRT-P is used only in NYHA class III/IV and QRS duration ≥120ms), direct comparisons of these survival estimates should not be made.

The values in this table are used to predict the proportion of the incident populations who are alive at subsequent years (and hence incur the costs presented in Table 92). For example, someone who gets an ICD will have a 92.9% chance of living one year, an 85.3% chance of living two years, and so on.

Table 93: Survival estimates used in the financial impact assessment

	Year 1	Year 2	Year 3	Year 4	Year 5
ICD	92.9%	85.3%	78.1%	71.2%	64.9%
CRT-P	86.9%	74.1%	62.7%	53.0%	44.7%
CRT-D	93.1%	85.8%	78.8%	72.1%	66.0%

7.4 Results

7.4.1 Scenario 1: 25% increase on current projections for ICD usage

The outputs from the model are presented in Table 94. The annual budgetary increase ranges from £41.6 million in year 1 to £69.9 million in year 5.

Table 94: Budget impact analysis: Scenario one

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£236,990,204	£267,092,765	£299,352,673	£336,036,417	£375,008,423
Total budget impact	£41,627,873	£47,176,815	£53,512,209	£60,893,306	£68,867,122

7.4.2 Scenario 2: 50% increase on current projections for ICD usage

The outputs from the model are presented in Table 95. The annual budgetary increase ranges from £59.4 million in year 1 to £91.9 million in year 5.

Table 95: Budget impact analysis: Scenario two

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£254,793,949	£285,988,507	£319,519,948	£357,617,274	£398,062,007
Total budget impact	£59,431,618	£66,072,557	£73,679,484	£82,474,163	£91,920,707

7.4.3 Scenario 3: 100% increase on current projections for ICD usage

The outputs from the model are presented in Table 96. The annual budgetary increase ranges from £95.0 million in year 1 to £138.0 million in year 5.

Table 96: Budget impact analysis: Scenario three

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£290,401,439	£323,779,992	£359,854,498	£400,778,988	£444,169,177
Total budget impact	£95,039,108	£103,864,042	£114,014,033	£125,635,877	£138,027,876

7.4.4 Scenario 4: 200% increase on current projections for ICD usage

The outputs from the model are presented in Table 97. The annual budgetary increase ranges from £166.3 million in year 1 to £230.2 million in year 5.

Table 97: Budget impact analysis: Scenario four

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£361,616,418	£399,362,962	£440,523,597	£487,102,416	£536,383,515
Total budget impact	£166,254,087	£179,447,012	£194,683,133	£211,959,305	£230,242,215

7.4.5 Discussion of model outputs

Depending on the choice of scenario and year of interest, the additional annual expenditure incurred by the NHS ranges from £41.6 million to £230.2 million per year. Actual annual values will be somewhere between the derived values in each of the tables above. However, the key fact that needs to be considered

when interpreting these results is that the majority of interventions were shown to be cost-effective in the groups where they are indicated.

7.5 Implications to other interested stakeholders

In terms of implications to other parties, as noted by Fox *et al.*[34] in their 2007 assessment:

"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.

Clinical advisors have suggested that: (1) the current availability of cardiologists with the necessary skills to undertake CRT surgery is one to two per regional centre, 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."

We believe the views expressed in this statement are still relevant.

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Association of British Healthcare Industries

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)

Appendices

6th July 2012

Appendix 1: Search strategies used to identify RCTs

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>

Search run on 27/06/2011

1 (CRT or "cardiac resynchron$ therap$").tw. (6517)
2 resynchron$ therap$.tw. (2829)
3 BVP.tw. (170)
4 Cardiac Resynchronization Therapy/ (228)
5 (biventricular adj10 pac$).tw. (1261)
6 (biventricular adj10 stimulat$).tw. (157)
7 ((cardiac or heart) adj10 resynch$).tw. (3034)
8 (coronary adj10 resynch$).tw. (131)
9 (atriobiventricular adj10 pac$).tw. (14)
10 (atrio biventricular adj10 pac$).tw. (23)
11 CRT-P.tw. (133)
12 CRT-D.tw. (176)
13 cardioversion.tw. (4098)
14 cardioverter.tw. (6545)
15 Defibrillators, Implantable/ (8786)
16 (internal adj3 (defibrillat$ or cardioverter)).tw. (422)
17 (implant adj3 (cardioverter or defibrillat$)).tw. (122)
18 (cardiac adj3 defibrillat$).tw. (1061)
19 ((implant or internal or cardiac) and defib$).tw. (7618)
20 icd.tw. (14797)
21 or/1-20 (35301)
22 Intraventricular conduction delay$.tw. (271)
23 Dilated cardiomyopathy.tw. (10812)
24 (Sudden death adj3 cardiac).tw. (801)
25 ((prolonged or wide) adj2 QRS).tw. (1056)
26 (Premature ventricular adj1 (complex$ or contraction)).tw. (794)
27 ((Reduced or low) adj ejection fraction).tw. (1045)
28 ((impaired or dysfunction or function) adj3 (left ventric$ or LVEF or LV)).tw. (37111)
29 (ventricular adj1 (tachycardia or fibrillation)).tw. (25008)
30 arrhythmi$.tw. (57496)
31 heart failure.tw. (85570)
32 ((cardiac or ventricular or intraventricular) adj5 asynchron$).tw. (444)
33 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).tw. (882)

34 cardiac arrest.tw. (16215)

35 tachycardia, ventricular/ (8877)

36 Arrhythmias, Cardiac/ (47995)

37 Heart Failure/ (71586)

38 Death, Sudden, Cardiac/ (9017)

39 Ventricular Dysfunction, Left/ or Bundle-Branch Block/ (23476)

40 Bundle Branch Block.tw. (6055)

41 Ventricular Fibrillation/ (13640)

42 Heart Arrest/ (19743)

43 Myocardial Infarction/ (126739)

44 or/22-43 (368895)

45 Randomized controlled trials as Topic/ (73673)

46 Randomized controlled trial/ (309567)

47 Random allocation/ (71762)

48 Double blind method/ (110773)

49 Single blind method/ (15106)

50 Clinical trial/ (463846)

51 exp Clinical Trials as Topic/ (242485)

52 clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or multicenter study/ (558228)

53 or/45-52 (851498)

54 randomized controlled trial.pt. (309567)

55 controlled clinical trial.pt. (82654)

56 random allocation.sh. (71762)

57 double blind method.sh. (110773)

58 single blind method.sh. (15106)

59 (clin$ adj25 trial$).tw. (200910)

60 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).tw. (114910)

61 Placebos/ (29766)

62 Placebo$.tw. (133939)

63 Random$.tw. (553900)

64 or/54-63 (914706)

65 53 or 64 (1220129)

66 Case report.tw. (168393)

67 Letter/ (733158)

68 Historical article/ (275454)

69 or/66-68 (1167008)

70 65 not 69 (1192243)

71 21 and 44 and 70 (3760)

72 animals/ not (animals/ and humans/) (3520949)

73 71 not 72 (3508)

74 limit 73 to english language (3198)

75 limit 74 to yr="1990 -Current" (3152)

Database: Embase<1988 to 2011 Week 25>

Search run on 27/06/2011

1 (CRT or "cardiac resynchron$ therap$").tw. (9071)
2 resynchron$ therap$.tw. (4112)
3 BVP.tw. (178)
4 cardiac resynchronization therapy/ (5525)
5 (biventricular adj10 pac$).tw. (1670)
6 (biventricular adj10 stimulat$).tw. (219)
7 ((cardiac or heart) adj10 resynch$).tw. (4377)
8 (coronary adj10 resynch$).tw. (167)
9 (atrio biventricular adj10 pac$).tw. (30)
10 (atriobiventricular adj10 pac$).tw. (20)
11 CRT-P.tw. (242)
12 CRT-D.tw. (485)
13 cardioversion.tw. (4285)
14 cardioverter.tw. (7839)
15 (internal adj3 (defibrillat$ or cardioverter)).tw. (442)
16 (implant$ adj3 (cardioverter or defibrillat$)).tw. (9516)
17 (cardiac adj3 defibrillat$).tw. (1115)
18 ((implant or internal or cardiac) and defib$).tw. (8844)
19 icd.tw. (20125)
20 *defibrillator/ (6658)
21 or/1-20 (44411)
22 *Heart arrest/ (10051)
23 *myocardial infarction/ (48787)
24 *Death,-Sudden,-Cardiac/ (8275)
25 cardiac arrest.tw. (15652)
26 Intraventricular conduction delay$.tw. (280)
27 Dilated cardiomyopathy.tw. (12299)
28 (sudden death adj3 cardiac).tw. (818)
29 ((prolonged or wide) adj2 QRS).tw. (1190)
30 (Premature ventricular adj1 (complex$ or contraction)).tw. (699)
31 ((Reduced or low) adj ejection fraction).tw. (1302)
32 ((impaired or dysfunction or function) adj3 (left ventric$ or LVEF or LV)).tw. (39565)
33 (ventricular adj1 (tachycardia or fibrillation)).tw. (22091)
34 arrhythmi$.tw. (52667)
35 *congestive cardiomyopathy/ (5894)
36 *heart muscle conduction system/ (1786)
37 *heart arrhythmia/ (18228)

38 *heart bundle branch block/ (712)
39 *heart failure/ (39054)
40 *congestive heart failure/ (17950)
41 heart failure.tw. (96051)
42 ((cardiac or ventricular or intraventricular) adj5 asynchron$).tw. (464)
43 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).tw. (1299)
44 *Bundle-Branch Block/ (712)
45 Bundle Branch Block.tw. (4682)
46 *heartventricletachycardia/ (8113)
47 *syncope/ (5496)
48 *heartventricle fibrillation/ (5098)
49 or/22-48 (273295)
50 Clinical trial/ (758285)
51 Randomized controlled trial/ (265459)
52 Randomization/ (49808)
53 Single blind procedure/ (13620)
54 Double blind procedure/ (90508)
55 Crossover procedure/ (29846)
56 Placebo/ (146356)
57 Rct.tw. (6934)
58 random*.tw. (588686)
59 (clinical trial$ or controlled clinical trial$ or major clinical stud$ or controlled stud$).tw. (219539)
60 (clinical adj25 trial$).tw. (213401)
61 ((single$ or double$ or treble$ or triple$) and (blind$ or mask$)).tw. (117874)
62 Placebo$.tw. (137596)
63 Prospective study/ (157946)
64 or/50-63 (1381558)
65 Case study/ (10159)
66 Abstract report/ or letter/ (611863)
67 or/65-66 (621895)
68 64 not 67 (1352204)
69 21 and 49 and 68 (4664)
70 limit 69 to english language (4204)
71 animal/ not (animal/ and human/) (526120)
72 animal experiment/ (1040422)
73 71 or 72 (1559640)
74 70 not 73 (3995)
75 conference.so. (435795)
76 74 not 75 (3512)
77 limit 76 to yr="1990 -Current" (3499)

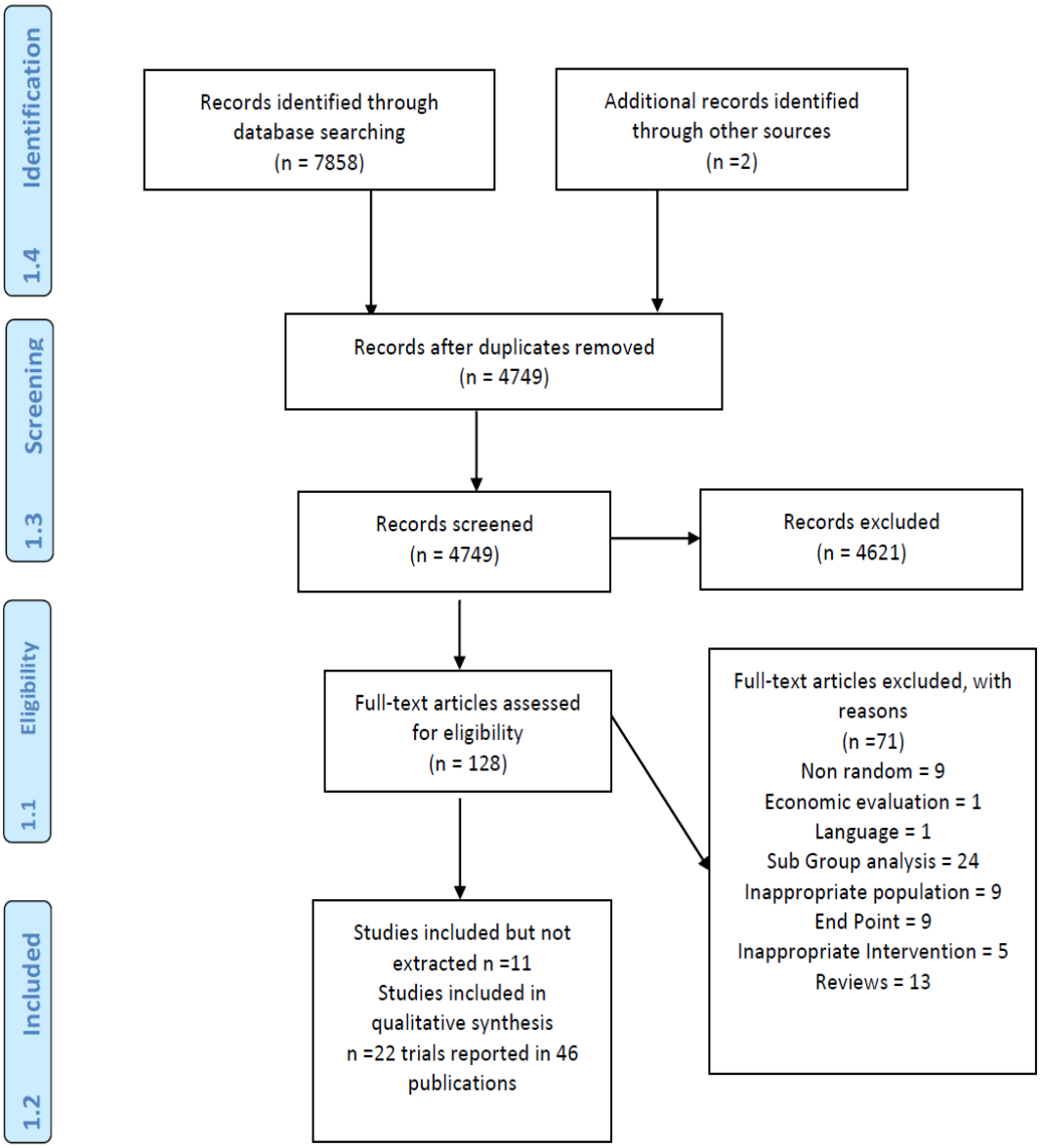
Database: Cochrane

Search run on: 28/06/2011

#1	(CRT or cardiac resynchron* therap*):ti,ab,kw in Clinical Trials	647
#2	(resynchron* therap*):ti,ab,kw in Clinical Trials	204
#3	(BVP):ti,ab,kw in Clinical Trials	14
#4	MeSH descriptor Cardiac Resynchronization Therapy, this term only	4
#5	(biventricular NEAR pac*):ti,ab,kw in Clinical Trials	108
#6	(biventricular NEAR stimulat*):ti,ab,kw in Clinical Trials	16
#7	((cardiac or heart) NEAR resynch*):ti,ab,kw in Clinical Trials	205
#8	(coronary NEAR resynch*):ti,ab,kw in Clinical Trials	3
#9	(atriobiventricular NEAR pac*):ti,ab,kw in Clinical Trials	3
#10	(atrio biventricular NEAR pac*):ti,ab,kw in Clinical Trials	11
#11	(CRT-P):ti,ab,kw in Clinical Trials	23
#12	(CRT -D):ti,ab,kw in Clinical Trials	58
#13	(cardioversion):ti,ab,kw in Clinical Trials	546
#14	(cardioverter):ti,ab,kw in Clinical Trials	470
#15	MeSH descriptor Defibrillators, Implantable, this term only	734
#16	(internal NEAR (defibrillat* or cardioverterter)):ti,ab,kw in Clinical Trials	19
#17	(implant NEAR (cardioverter OR defibrillat*)):ti,ab,kw in Clinical Trials	119
#18	(cardiac NEAR defibrillat*):ti,ab,kw in Clinical Trials	283
#19	((implant OR internal OR cardiac) AND defib*):ti,ab,kw in Clinical Trials	709
#20	(icd):ti,ab,kw in Clinical Trials	780
#21	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)	2746
#22	(intraventricular conduction delay):ti,ab,kw in Clinical Trials	31
#23	(Dilated cardiomyopathy):ti,ab,kw in Clinical Trials	551
#24	(Sudden death NEAR cardiac):ti,ab,kw in Clinical Trials	641
#25	((prolonged or wide) NEAR QRS):ti,ab,kw in Clinical Trials	84
#26	(Premature ventricular NEAR (complex* or contraction)):ti,ab,kw in Clinical Trials	415
#27	((Reduced or low) NEAR ejection fraction):ti,ab,kw in Clinical Trials	446

#28	((impaired or dysfunction or function) NEAR (left ventric* or LVEF or LV)):ti,ab,kw in Clinical Trials	4865
#29	(ventricular NEAR (tachycardia or fibrillation)):ti,ab,kw in Clinical Trials	1673
#30	(heart failure):ti,ab,kw in Clinical Trials	8459
#31	((cardiac or ventricular or intraventricular) NEAR asynchron*):ti,ab,kw in Clinical Trials	25
#32	((cardiac or ventricular or intraventricular) NEAR dyssynchron*):ti,ab,kw in Clinical Trials	56
#33	MeSH descriptor Arrhythmias, Cardiac, this term only	1604
#34	MeSH descriptor Heart Failure, this term only	4620
#35	MeSH descriptor Ventricular Dysfunction, Left, this term only	1412
#36	(Bundle Branch Block):ti,ab,kw in Clinical Trials	178
#37	(arrhythmi*):ti,ab,kw in Clinical Trials	5106
#38	(cardiac arrest):ti,ab,kw in Clinical Trials	990
#39	MeSH descriptor Heart Arrest, this term only	533
#40	MeSH descriptor Death, Sudden, Cardiac explode all trees	452
#41	MeSH descriptor Bundle-Branch Block explode all trees	79
#42	MeSH descriptor Ventricular Fibrillation explode all trees	425
#43	MeSH descriptor Myocardial Infarction explode all trees	7646
#44	(#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43)	23964
#45	(#21 AND #44), from 1990 to 2011	1418
#46	(#45)	1207

Appendix 2: Prisma Flow Diagram



Appendix 3: Assessment of risk of bias

All included studies were critically appraised following the criteria specified by NICE. This assessment requires the evaluation of individual components that affect risk of bias. This method is described in the Cochrane Handbook for Systematic Reviews and the Centre for Reviews and Dissemination guidance. In line with this method, the following items were appraised:

Description of randomisation:

A method of randomisation will be considered adequate when any pattern of allocation is equally likely. Examples of acceptable methods of randomisation include:

- The use of a computer random number generator

- Referring to a random number table

The description of randomisation will be regarded as unclear if there is insufficient information about the sequence generation process. For example, a study described as randomised but no method of randomisation is described.

Description of allocation concealment:

An adequate method of allocation concealment ensures patients and investigators are unaware of the forthcoming assignment. Examples of appropriate methods of allocation concealment include the following:

- Central allocation: telephone, pharmacy-controlled

- Sequentially numbered, opaque, sealed envelopes

- Sequentially numbered drug containers of identical appearance

Inadequate methods of allocation concealment include:

- the use of open random allocation schedule: list of random numbers
- use of non-opaque or not sequentially numbered envelopes
- allocation by alternation, date of birth

If there is insufficient information to assess the method of allocation concealment this will be regarded as unclear.

Blinding of participants, investigators and outcome assessors:

Criteria for an adequate method of blinding will be based on the following:

- Blinding of patients and investigators is ensured and unlikely that the blinding could have been broken.
- Either patients or investigators were not blinded but the outcome assessment was blinded (outcome adjudicated by a blinded events committee).

The following will be regarded as inadequate method of blinding:

- No blinding or incomplete blinding
- Study described as double blind but likely that blinding could have been broken

Method of blinding will be regarded as unclear if there is insufficient information to assess blinding. For example, a study described as double-blind but no description of blinding is provided.

Description of patients' baseline characteristics- whether the groups were similar at the outset of the study in terms of prognostic factors:

Adequate reporting should include a detailed description of the main prognostic factors of patients at baseline per treatment group and report any unbalances between the groups.

Inadequate description of patient's baseline characteristics will include: no description or insufficient information of patient's baseline characteristics or details provided for the whole group of patients in the study rather than per treatment arms.

Intention-to-treat analysis

Very often, patients enrolled in a randomised trial do not receive the study treatment to which they were randomised or are withdrawn from the study. An intention-to-treat (ITT) analysis includes data on all trial patients and analyses them according to the intervention to which they were randomised.

While it is possible to analyse data of patients according to the intervention groups they were allocated to, it is not always possible to measure outcome data

on all the patients due to withdrawals and drop-outs. For this reason a true ITT analysis cannot be performed without making assumptions about missing outcome data.

It is common for authors to report an ITT analysis even though some outcome data are missing.

An ITT analysis will be regarded as adequate if there is a statement confirming that the analysis was based on ITT or if it is clear from the text that data from patients were analysed according to the intervention group they were randomised. As regards whether appropriate methods were used to account for missing data, we will highlight where there is a high proportion of missing outcomes or large difference between groups.

Table 1: Assessment of risk of bias of included studies

Study reference	Reporting of randomization	Reporting of allocation concealment	Reporting of blind treatment assignment/ blind outcome assessment	Description of pts. baseline characteristics/ group balance	Analysis based on ITT
AMIOVIRT	Unclear	Unclear	Adequate	Adequate	Adequate
CARE-HF	Adequate	Adequate	Adequate	Adequate	Adequate
CAT	Unclear	Adequate	Unclear	Adequate	Unclear
COMPANION	Unclear	Unclear	Adequate	Adequate	Adequate
Contak-CD	Unclear	Unclear	Unclear	Adequate	Unclear
DEFINITE	Unclear	Unclear	Adequate	Adequate	Adequate
MADIT	Unclear	Unclear	Unclear	Adequate	Adequate
MADIT-CRT	Unclear	Adequate	Adequate	Adequate	Adequate
MADIT II	Unclear	Adequate	Unclear	Adequate	Adequate
MIRACLE	Unclear	Adequate	Adequate	Adequate	Adequate
MIRACLE-ICD	Adequate	Adequate	Adequate	Adequate	Adequate
MIRACLE-ICD II	Adequate	Adequate	Adequate	Adequate	Adequate
MUSTIC	Unclear	Unclear	Inadequate	Adequate	Adequate
Piccirillo et al	Unclear	Unclear	Unclear	Adequate	Unclear
Pinter et al	Unclear	Unclear	Adequate	Adequate	Unclear
RAFT	Unclear	Adequate	Adequate	Adequate	Adequate
RESPOND	Adequate	Adequate	Unclear	Adequate	Adequate
RETHINQ	Adequate	Adequate	Adequate	Adequate	Adequate
REVERSE	Unclear	Unclear	Adequate	Adequate	Adequate
RHYTHM ICD	Unclear	Unclear	Unclear	unclear	Unclear
SCD- HeFT	Unclear	Unclear	Adequate	Adequate	Adequate
Vector	unclear	Unclear	Unclear	unclear	unclear

Appendix 4: List of secondary prevention trials

AVID

A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. The New England journal of medicine 1997;337:1576-83.

Causes of death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. Journal of the American College of Cardiology 1999 Nov 1;34(5):1552-9.

Antiarrhythmics Versus Implantable Defibrillators (AVID)--rationale, design, and methods. American Journal of Cardiology 1995 Mar 1;75(7):470-5.

CIDS

Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.

Connolly SJ, Gent M, Roberts RS, Dorian P, Green MS, Klein GJ, et al. Canadian implantable defibrillator study (CIDS): Study design and organization. American Journal of Cardiology 1993;72(16):103F-8F.

MAVERIC

Lau EW, Griffith MJ, Pathmanathan RK, Ng GA, Clune MM, Cooper J, et al. The Midlands Trial of Empirical Amiodarone versus Electrophysiology-guided Interventions and Implantable Cardioverter-defibrillators (MAVERIC): a multi-centre prospective randomised clinical trial on the secondary prevention of sudden cardiac death. Europace : European pacing, arrhythmias , and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias , and cardiac cellular electrophysiology of the European Society of Cardiology 2004;6:257-66.

CASH

Siebels J, Kuck K-H. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). American Heart Journal 1994;127(4 II SUPPL.):1139-44

Siebels J, Cappato R, Ruppel R, Schneider MAE, Kuck KH, Kalmar P, et al. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). American Journal

of Cardiology 1993;72(16):109F-13F.

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Appendix 5: Reported adverse events

Table 2- Adverse events reported in the AMIOVERT trial (n, % unless otherwise stated)

Event	Occurrences
ICD arm	
Received amiodarone for the following reasons:	
Atrial fibrillation	8 (15.69)
Frequent appropriate defibrillator therapies requiring amiodarone	1 (1.96)
Other reasons	2 (3.92)
Underwent cardiac transplantation (reason not reported)	1 (1.96)
OMT arm	
Adverse events after initiation of therapy	
These patients had their drug discontinued because of adverse events[1]	25 (48.08)
Adverse events after 26.1 (16.9) months of entry the trial	
An ICD was inserted in 8 patients for the following reasons:	
Near- syncope	2 (3.85)
Cardiac arrest	2 (3.85)
Amiodarone intolerance	4 (7.69)
Underwent cardiac transplantation (reason not reported)	2 (3.85)

n = patients in the group reporting an adverse event **1**-Full details of the particular adverse event experienced by the 25 patients were not provided.

Table 3- Adverse events reported in the CARE-HF trial (n, % unless otherwise stated)

Event	Occurrences
OMT arm	
Device related death	
Septicemia after receiving a device	1 (0.25)
Other adverse events	
Worsening heart failure	263 (65.10)
Atrial arrhythmias/ ectopy	41(10.15)
CRT-P arm	
Device related death	
Death from Heart failure aggravated by lead displacement	1 (0.24)
Most common device or procedure related adverse events	
lead displacement	24 (5.87)
coronary- sinus dissection	10 (2.44)
pocket erosion	8 (1.96)
pneumothorax	6 (1.47)
device related infection	3 (0.73)
Other adverse events	
Worsening heart failure	191(46.69)
Atrial arrhythmias/ ectopy	64 (15.65)

NB: The frequency of respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmias or ectopy, and neurologic events were similar in the two groups (OMT vs. CRT-P).

Table 4- Adverse events reported in the CAT trial (n, % unless otherwise stated)

Event	Occurrences
ICD arm	
Complications within 30 days of device implantation	
Device dislocation	1
Bleeding	1
Electrode dislocation revised by surgery	2
Complications during long term follow up (24 months)	
10 complications occurred in 7 (14%) patients	
Electrode dislocation & sensing isolation	7
Infections	2
Perforation	1
OMT arm	
Complications were only reported for the ICD arm	

Table 5- Adverse events reported in the COMPANION trial (n, % unless otherwise stated)

Event	Occurrences
CRT-D arm	
Moderate or severe adverse event related to the implantation procedure	
Moderate or severe adverse events related to the implantation procedure occurred in 8 % of patients including the following	
Coronary venous dissection	0.5%
Coronary venous perforation	0.8%
Coronary venous tamponade	0.3%
CRT-P arm	
Moderate or severe adverse event related to the implantation procedure	
Moderate or severe adverse event related to the implantation procedure occurred in 10% of patients including the following:	
Coronary venous dissection	0.3%
Coronary venous perforation	1.10%
Coronary venous tamponade	0.5%
OMT arm	
Details of individual adverse events were not reported. However, the author reported that a total of 61% of the patients in this arm experienced moderate to severe adverse event from any cause.	

NB: in the CRT-D arm a total of 69% patients experienced moderate to severe adverse events from any cause. However, full details of these were not provided. In the CRT-P arm a total of 66% of patients experienced moderate or severe adverse event from any cause. However, full details were again not provided.

Table 6- Adverse events reported in the CONTAK-CD trial (n/N)

Event	Occurrences
Adverse events during implantation	
Placement of coronary venous lead failure	66/567[1]
Other adverse event (within the 30-day post-implant recovery period)	
Death due to pump failure	5/501[2]
Death due to pulseless electrical activity resulting from defibrillation threshold	1/501[2]
Death due to incessant ventricular tachycardia	1/501[2]
Death due to cardiac cause	1/501[2]
Death from unknown cause	1/501[2]

1- total number patients with an implant attempt. 2- successfully implanted patients. n = number of patients in the arm reporting an adverse event

Table 7- Adverse events reported in the DEFINITE trial (n, % unless otherwise stated)

Event	Occurrences
ICD arm	
Complications during the implantation of the ICD 3 (1.3%)	
Haemothorax	1 (0.43%)
Pneumothorax	1 (0.43%)
Cardiac tamponade	1 (0.43%)
Complications during the long term follow up phase 10 (4.4%)	
Lead dislodgement or fractures	6 (2.62%)
Venous thrombosis	3 (1.31%)
Infection	1 (0.43%)
ICD upgrades	13 (5.68%)
Development of Sinus-node dysfunction requiring dual chamber ICDs	2 (0.87%)
NYHA class III/IV heart failure and prolonged QRS Interval requiring biventricular device	11 (4.80%)
OMT arm	
Received ICDs due to syncope or heart failure and prolong QRS interval	23 (10.04)

Table 8- Adverse events reported in the MADIT trial (n, % unless otherwise stated)

Event	Occurrences
ICD arm	
The total number of patients with adverse events was 19 (20%)	
Syncope	1 (1.05%)
Sinus bradycardia	3 (3.16%)
Pulmonary embolism	1 (1.05%)
Atrial fibrillation	4 (4.21%)
Pneumothorax	2 (2.10%)
Bleeding	1 (1.05%)
Venous thrombosis	1 (1.05%)
Surgical infection	2 (2.10%)
Problems with defibrillator lead	7(7.37%)
Malfunction of defibrillator generator	3 (3.16%)
OMT arm	
The total number of patients with adverse events was 12 (12%)	
Hypotension	1 (0.99%)
Syncope	5 (4.95%)
Hypothyroidism	1 (0.99%)
Sinus bradycardia	3 (2.97%)
Pulmonary fibrosis	3 (2.97%)
Pulmonary embolism	1 (0.99%)
Malfunction of defibrillator generator	2 (1.98%)

Table 9- Adverse events reported in the MADIT II trial (n, % unless otherwise stated)

Event	Occurrences
ICD arm	
Device related adverse events	
Lead related problems requiring surgical intervention	13 (1.8 %)
Non-fatal infection requiring surgical intervention	5 (0.7 %)
Non-Device related adverse events	
Worsening heart failure requiring Hospitalization	148 (19.9%)
OMT arm	
Worsening heart failure requiring Hospitalization	73 (14.90%)

Table 10- Adverse events reported in the MADIT-CRT trial (n, % unless otherwise stated)

Event	Occurrences
CRT-D arm	
The total number of patients with adverse events was 19 (20%)	
Adverse event during hospitalisation after device implantation	
Death due to pulmonary embolus documented on autopsy	0.09%
Adverse event within 30 days of device implantation	
Pneumothorax	1.7%
Infection	1.1%
Pocket hematoma requiring evacuation	3.3%
Left ventricular coronary-vein reposition	4%
Adverse event during CRT-D implantation	
Coronary venous dissection with pericardial effusion	0.5%
ICD arm	
Adverse event within 30 days of device implantation	
Pneumothorax	0.8%
Infection	0.7%
Pocket hematoma requiring evacuation	2.50%

NB: during long term follow up after first 30 days in the CRT-D arm, serious device related adverse events occurred with a frequency of 4.5 per 100 device months and in the ICD arm serious device related adverse events occurred with a frequency of 5.2 per 100 device months

Table 11- Adverse events reported in the MIRACLE trial (n, % unless otherwise stated)

Event	Occurrences
CRT-P arm	
Adverse event during Implantation procedure	
Complete heart block requiring permanent cardiac pacing	2 (0.35)
Progressive hypotension	1 (0.18)
Asystole needing cardiopulmonary resuscitation	1 (0.18)
Coronary sinus dissection	23 (4.03)
Coronary vein or coronary sinus perforation	12 (2.10)
Adverse event after implantation	
Left ventricular lead reposition	20 (3.79)
Left ventricular lead replacement	10 (1.89)
Pacemaker related infection requiring explanation	7 (1.33)

NB: There was no significant difference in the frequency of adverse event unrelated to the device or heart failure between the two treatment groups

Table 12- Adverse events reported in the MIRACLE-ICD trial (n, % unless otherwise stated)

Event	Occurrences
CRT-D arm	
From implant to hospital discharge	
Left ventricular lead related	37 (23%)
Coronary sinus dissection	15 (9.4%)
Cardiac perforations	4 (2.5%)
Heart failure decompensation	6 (3.8%)
Heart block	3 (1.9%)
Muscle stimulation	4 (2.5%)
Pericardial effusion	2 (1.3%)
Pericarditis	1 (0.6%)
Ventricular tachycardia/ventricular fibrillation	5 (3.1%)
Haemothorax/pneumothorax	3 (1.9%)
Elevated pacing/loss of capture	7 (4.4%)
Post discharge in non-randomised CRT systems implanted (n=10)	
Left ventricular lead related	3 (10.7%)
ICD systems related	0
Procedure related	3 (10.7%)
Heart failure decompensation	7 (25.0%)
Other	15 (53.6%)
Post-discharge in non-randomised unsuccessful CRT systems implant patients (n=50)	
Procedure related	1 (2.9%)
Heart failure decompensation	19 (54.3%)
Other	15 (42.9%)
Post-discharge in randomised CRT-ON patients (n=187)	
Left ventricular lead related	21 (11.4%)
ICD systems related	9 (4.9%)
Procedure related	10 (5.4%)
Heart failure decompensation	63 (34.2%)
Other	81 (44.0%)
ICD arm (CRT-OFF)	
Post-discharge in randomized/ successfully implanted patients (n=182)	
Left ventricular lead related	14 (7.5%)
ICD systems related	14 (7.5%)
Procedure related	13 (7.0%)
Heart failure decompensation	71 (38.2%)
Other	74 (39.8%)

Table 13- Adverse events reported in the MADIT-ICD-II trial (n, % unless otherwise stated)

Event	Occurrences
CRT-D arm	
Among the 210 patients undergoing a CRT-D implant attempt, 46 (22%) patients experienced a total of 56 complications from the time of implant to hospital discharge *which include the following*	
Complications during implant attempt	
Left ventricular lead related	19 (34%)
Coronary sinus dissections	3 (5.3%)
Cardiac perforations	3 (5.35%)
Lead dislodgement	5 (8.9%)
23 patients failed their initial attempt; 4 eventually receiving a CRT-D system	
Complications from hospital discharge to end of randomization period	
66 (35%) of 191 patients with successful CRT-D implant, experienced 109 complications which include the following:	
Left ventricular lead related	19(17%)
Lead dislodgements	11(10.09%)
Cardiac perforations	1 (0.92%)
Diaphragmatic muscle stimulation	3 (2.75%)
Elevated pacing thresholds	4 (3.67%)

Table 14- Adverse events reported in the MUSTIC trial (n, % unless otherwise stated)

Event	Occurrences
Uncorrectable loss of left ventricular pacing efficacy and did not complete the two crossover periods.	2
Inactive pacing	
Severe decompensation leading to a premature switch to active pacing	1
Decompensation due to atrial fibrillation	1
Active pacing	
Sudden death	1
Decompensation due to rapidly progressive aortic stenosis	1
Death from acute myocardial infarction a few hours after a premature switch to active pacing because of severe decompensation	1
Sudden death after switching from inactive to active	1

Table 15- Adverse events reported in Picorillo et al. (n, % unless otherwise stated)

Event	Occurrences
Major complications following implantation	0
Of the 15 patients randomised to the ICD group 2 (13.3%) were hospitalised due to worsening of heart failure	

Table 16- Adverse events reported in Pinter et al. (n, % unless otherwise stated)

Event	Occurrences
Of the 90 attempted implants, 75 (83.3%) were successful	
Acute procedural related complications included:	
Haematoma	1(1.11%)
Right ventricular lead failure requiring replacement	1(1.11%)
Device related complications in successfully implanted patients	
Of the 75 successful implants, 2 patients (2.6%) were not randomised due to device-related technical difficulties (double sensing)	
CRT-ON	
late Left ventricular capture failure	1(2.78%)
death due to cardiac cause	1(2.78%)
CRT-OFF	
Worsening congestive heart failure	1(2.78%)
Death from cardiac cause	1(2.78%)

Table 17- Adverse events reported in the RAFT trial (n, % unless otherwise stated)

Event	Occurrences
CRT-D arm	
Of the 894 patients in the CRT-D group, 888 (99.3%) underwent device implantation. Reasons for non-implantation included 4 cases in which the patient died and 2 cases in which the patient or physician declined to participate.	
Device or implantation related complications (first 30 days)	
There were 118 device or implantation related complications among 888 patients receiving CRT-D, including:	
Device pocket haematoma requiring intervention	14 (1.6%)
Haemothorax/pneumothorax	11 (1.2%)
Device pocket infection requiring intervention	21 (2.4%)
Lead dislodgement requiring intervention	61 (6.9%)
Device pocket problems requiring revision	4 (0.5%)
Coronary sinus dissection	11 (1.2%)
ICD arm	
Of the 904 patients in the ICD group, 899 (99.4%) underwent device implantation. Reasons for non-implantation included 4 cases in which the patient or physician declined to participate and 1 case in which there was a lack of venous access.	
Adverse event within 24hours after device implantation	
Death from worsening heart failure	8 (0.9%)
Device or implantation related complications (first 30 days)	
There were 61 device or implantation related complications among 899 patients in the ICD arm. These included:	
Haemothorax/pneumothorax	8 (0.9%)
Device pocket haematoma requiring intervention	11 (1.2%)
Device pocket infection requiring intervention	16 (1.8%)
Lead dislodgement requiring intervention	20 (2.2%)
Device pocket problems requiring revision	1 (0.1%)

Table 18- Adverse events reported in the RESPOND trial. (n, % unless otherwise stated)

Event	Occurrences
Adverse events not reported	

Table 19- Adverse events reported in the RETHINQ trial (n, % unless otherwise stated)

Event	**Occurrences**
Implant attempt patients	
Deep vein thrombosis	3 (1.70)
Pneumothorax	2 (1.20)
Pericarditis	2 (1.20)
Coronary sinus perforation	1 (0.60)
Lead dislodgement	13(7.60)
Infection	6 (3.50)
bleeding/ haematoma	2 (1.20)
loss of pacemaker lead capture	2 (1.20)
Phrenic-nerve stimulation	3 (1.70)
CRT arm	
There were 24 heart-failure events requiring intravenous therapy in 14 patients (16.1%)	
ICD *arm*	
There were 41 heart failure events requiring intravenous therapy in 19 patients (22.3%)	

Table 20- Adverse events reported in the REVERSE trial (n, % unless otherwise stated)

Event	Occurrences
During or just before implantation	
There were 26 procedure or system-related complications among the 642 patients who underwent an implant attempt:	
Adverse drug reaction	4(15.38)
Pneumothorax	4(15.38)
Atrial fibrillation or flutter	4(15.38)
Coronary sinus dissection	3(11.54)
Pulmonary Oedema	2(7.69)
Ventricular Fibrillation	2(7.69)
Complete heart block	2(7.69)
Cardiac Tamponade	1(3.85)
Pericardial effusion	1(3.85)
Electromechanical dissociation	1(3.85)
Hypotension	1(3.85)
Increased defibrillation threshold	1(3.85)
Procedure or system related adverse event after implantation	
After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients experienced a total of 138 procedure or system-related complications (postoperative procedure or system-related complication rate was 16%). Of these the most common postimplant complications were:	
Left ventricular lead dislodgement	41(29.71)
Right ventricular lead dislodgement	15(10.87)
Right atrial lead dislodgement	10(7.25)
Diaphragmatic muscle stimulation	14(10.14)
Atrial fibrillation or flutter	8(5.80)
Implant site haematoma	5(3.62)
Hypotension	4(2.90)
Pericardial effusion	4(2.90)
System related adverse event during 12 months of follow up	
Among the 621 successfully implanted patients during the first 12 months there was one CRT therapy-related complication in which cardiac failure was resolved by turning CRT off.	
There were 66 left ventricular lead complications among 59 patients (left ventricular lead related complications rate was 10%) which required reoperation in 48 patients (8% of successfully implanted patients). The most common events in the 66 left ventricular lead related complications were:	
Left ventricular lead dislodgement	41(62.12)
Diaphragmatic muscle stimulation	14(21.21)
Subclavian vein thrombosis	3(4.55)

Table 21- Adverse events reported in the RHYTHM-ICD trial (n, % unless otherwise stated)

Event	Occurrences
A total of 97 adverse events were reported in 70 patients, of which 29 were complications and 68 were observations	
Complications[1]	
Coronary sinus perforation/dissection	2
Diaphragmatic/Phrenic nerve stimulation	3
Lead dislodgement or migration	9
Bleeding/hematoma	6
Blood clot/thrombosis	1
High defibrillation/cardioversion requirements	2
Infection	1
Noise on EGM post shock (non-SJM RV lead)	1
Pneumothorax	2
Retained foreign body (surgical sponge)	1
Elevated pacing threshold- LV lead	1
Observations[2]	
Asystolic episode during LV lead placement	1
Bleeding/haematoma	10
Blood clot/thrombosis	2
Coronary sinus perforation/dissection	6
Diaphragmatic/phrenic nerve stimulation-LV lead	10
Diaphragmatic/phrenic nerve stimulation-RV lead	2
Heart block at implant	2
High defibrillation/cardioversion requirements	1
Hypotension requiring ventilator support	1
Inappropriate therapy for SVT	10
Infection	3
Possible pulmonary embolism	1
T-Wave sensing	2
Pocket inflammation/seroma	1

1- defined as adverse events that require invasive intervention; 2- defined as adverse events that can be managed without invasive intervention

Table 22- Adverse events reported in the SCD-HeFT trial (n, % unless otherwise stated)

Event	Occurrences
ICD arm	
Clinically significant complications[1] at the time of implantation	41 (5)
Clinically significant post-operative complications[1]	75 (9)
Amiodarone and placebo arms	
The only complications observed in the amiodarone group, as compared with the placebo group were increased tremor (4%) and increased hypothyroidism (6%)	

1- Clinical events requiring surgical correction, hospitalisation or new and otherwise unanticipated drug therapy.

Appendix 6: Multiple imputation approach (All-cause mortality)

Multiple imputations were created to impute values for the following variables (numbers in brackets denote number of instances in which values were missing): age ([redacted]); gender ([redacted]); NYHA ([redacted]); QRS ([redacted]); LVEF ([redacted]); Ischemia ([redacted]) and LBBB (229).

The imputation was carried out in the Amelia package[1]. Five imputed data sets were created. The approach used assumes that the complete (unobserved) data set has a multivariate normal distribution and that data are missing at random. Draws from the estimated complete data multivariate normal distribution are made using a combination of an expectation-maximisation algorithm and bootstrapping.

A description of the variables included in the imputation process is provided as Table 23.

Table 23: Variables included in imputation process

Variables included in analysis and imputation	Variables included in imputation only[a]	Variables included in analysis only
Time to death or loss to follow-up	Randomisation date	Device type – conditional upon study this should not be related to outcomes due to randomisation
Whether death or loss to follow-up	Weight	
Gender	Height	
Age	History of MI	Study – the model did not converge when STUDY dummy variables were included, presumably due to the collinearity of the 'study' and other independent variables.
NYHA	History of diabetes	
QRS	History of stroke	
LVEF	Systolic blood pressure	
Ischemia	6 minute hall walk	
LBBB	Receiving diuretics at baseline	
US	Receiving ACEI/ARB at baseline	
	Receiving beta-blockers at baseline	
	Receiving statins at baseline	
	RBBB	
	Prior ICD	

a) the following variables were collected in the data shell but not included in the imputations algorithm

[1] http://cran.r-project.org/web/packages/Amelia/vignettes/amelia.pdf

(with reasons): Patient ID (not predictive); Date of implant (highly correlated with date of randomisation); Diuretic name and dose/cause of death/creatinine (data not clean); Diastolic Blood Pressure (highly correlated with systolic blood pressure); Prior CRT (no patients were recorded to have had a prior CRT); History of spontaneous VT or VF/History of spontaneous, sustained VT/History of VF (data not thought to be consistently recorded across studies); Cross-over (would have to be treated as survival variable in which case too highly correlated with follow-up); Date of heart failure diagnosis/history of atrial tachycardia/receiving allopurinol at baseline/cholesterol/haemoglobin/lymphocytes/uric acid/date of last hospitalisation/brain natriuretic peptide/history of atrioventricular node ablation/history of ventricular flutter/history of atrial fibrillation/history of atrial flutter/sodium (all had very high levels of missingness [redacted] and were therefore excluded).

The graphs below display the predicted and observed values for QRS and LVEF, the only continuous covariables with a substantive number of missing values. The black lines depict the distribution of observed values. The red lines depict the distribution of imputed values. The graphs suggest that the imputation algorithm is imputing reasonable values for these variables.

[redacted]

Appendix 7: Explanation for absence of covariate adjusted random effects analysis (All-cause mortality)

Two alternative approaches to running the network meta-analysis were considered:

1. Stratified Cox proportional hazards model using all IPD (approach followed)
2. Two-stage approach (alternative approach considered) – this would have involved fitting individual Cox proportional hazards regressions to each trial. These could then have been used to generate trial specific hazard ratios for each covariable pattern (patient profile). These hazard ratios could then have been synthesised using a standard network meta-analysis approach for aggregate data.

Theoretically both approaches could be run as random effects analyses. However, for approach (1) this is not thought to be possible using standard frequentist software (e.g. R, SAS). It would be possible to run this analysis as a random effects model using Bayesian software (e.g. WinBUGS) however this would be computationally expensive. The exact run time is not predictable but would be expected to run to days or weeks for a database of this size. A previous analysis recorded run times of 41 seconds for 1,000 iterations on a database of 42 patients with 17 distinct event times (http://www.mrc-bsu.cam.ac.uk/bugs/documentation/exampVol1/node29.htm) whereas our database includes over 12,638 patients and 1,700 distinct event times). In addition, the benchmark analysis was not stratified.

Despite the potential to run a random effects version of option (2) easily, a number of problems with this approach were identified. The requirement to run separate regressions for each trial would have greatly reduced the power of the analysis to detect treatment effect modifiers. In addition, where treatment effect modifiers differed across analyses of different trials, difficult judgement calls regarding the final covariable set would have been required. The approach would also involve fitting a large number of parameters to the data set, reducing precision. Finally, this approach would not have generated a single estimate of

treatment effect modification, making the resulting models difficult to clinically validate. We concluded the advantage of approach (1) were sufficient to offset the disadvantage of not having a random effect version of the model.

Appendix 8 – Further detail regarding covariable-adjusted IPD network meta-analysis model

Equations (1) and (2) describe the difference between the model fitted without and with covariables as treatment effect modifiers.

- Equation 1 – unadjusted. This model is the stratified Cox PH model unadjusted for treatment effect modifiers. This model contains only dummy variables for each of the devices (CRT-P, CRT-D and ICD) and takes the following form:
- $\lambda_{ij} = \lambda_{oj}(t)\exp(\beta_{CRT-P}D_{CRT-P\ ij} + \beta_{CRT-D}D_{CRT-D\ ij} + \beta_{ICD}D_{ICD\ ij})$
- Where $\lambda_{ij}$is the hazard for the *ith* patient in the *jth* trial, the β's are the treatment coefficients expressing the efficacy of the devices relative to optimal pharmacological therapy (OPT) and the D's are the device specific dummy variables which take the value 1 if patient *i* in trial *j* was randomised to that device.
- Equation 2 – adjusted. This model is the stratified Cox PH model adjusted for treatment effect modifiers. This model contains dummy variables for each of the devices (CRT-P, CRT-D and ICD), covariable main effects and device by covariable interactions and takes the following form (assuming one covariable, though the formula is easily generalised to multiple covariables):
- $\lambda_{ij} = \lambda_{oj}(t)\exp(\beta_{cov}X_{covij} + \beta_{CRT-P}D_{CRT-P\ ij} + \beta_{CRT-D}D_{CRT-D\ ij} + \beta_{ICD}D_{ICD\ ij} + \beta_{inter.CRT-P}D_{CRT-P\ ij}X_{covij} + \beta_{inter.CRT-D}D_{CRT-D\ ij}X_{covij} + \beta_{inter.ICD}D_{ICD\ ij}X_{covij})$
- Where X_{covij} and β_{cov} are the covariable and coefficient on the covariable respectively and $\beta_{inter.DEV}$ is the coefficient on the device by covariable interaction.

Selection of covariables for inclusion in the final preferred model was based on the following exploratory analyses:

1. A review of univariate analyses - This involved including each covariable individually as a treatment effect modifier for all devices and reviewing

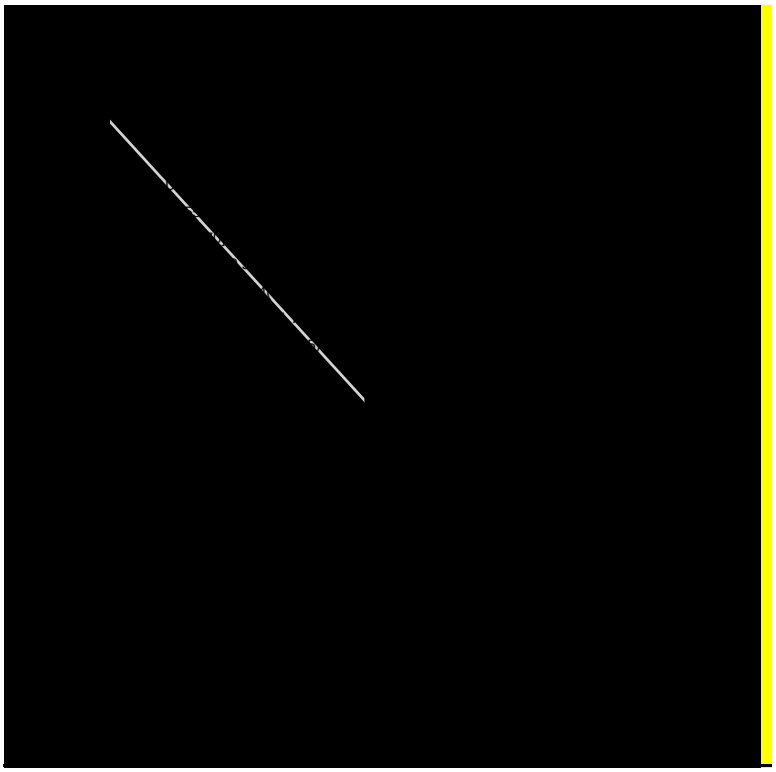
the results for statistical significance and clinically meaningful trends.

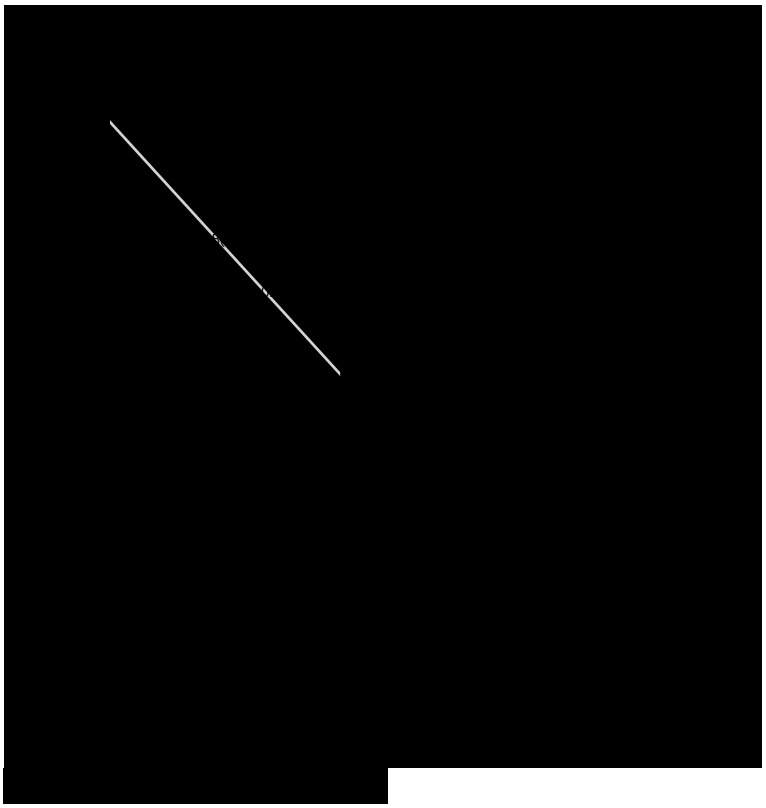
2. Multivariate analyses - a stepwise algorithm was used to select covariables for retention. A forward and backward selection algorithm based on Akaike's Information Criterion (AIC) with 2 degrees of freedom for the penalty was used. The stepwise procedure was run in two ways: once with treatment effect modifiers forced for all device treatment effects or none. The second analysis was more flexible and allowed the treatment effect modifiers to vary by device. This approach was thought to be clinically plausible as the devices act on different causes of mortality. The model was set up so that device by covariable interaction effects could only be included if the main covariable effects were included. The treatment main effects were forced in all models.

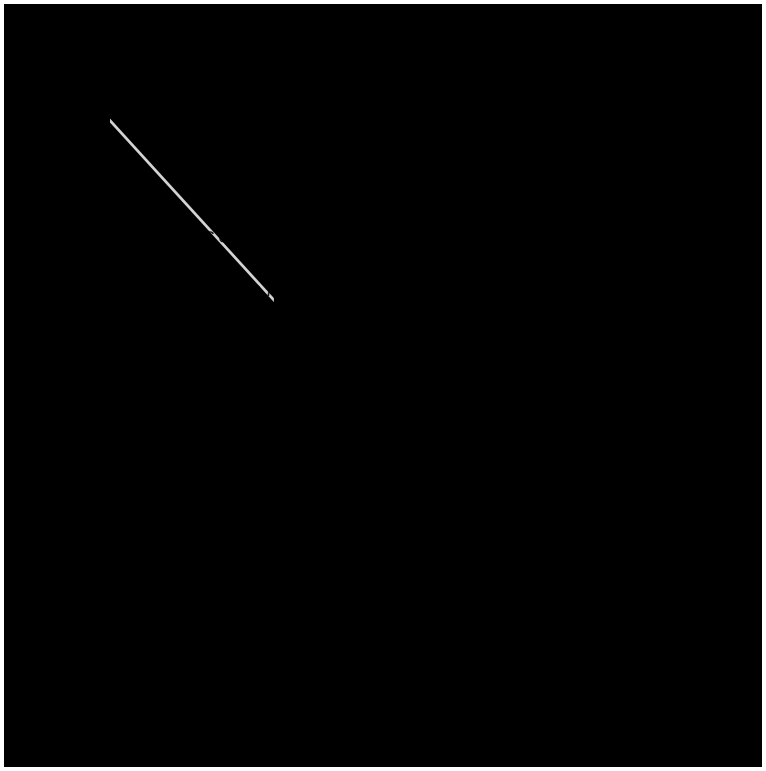
3. Clinical knowledge – These intermediary analyses were reviewed by two clinicians in order to assess their plausibility.

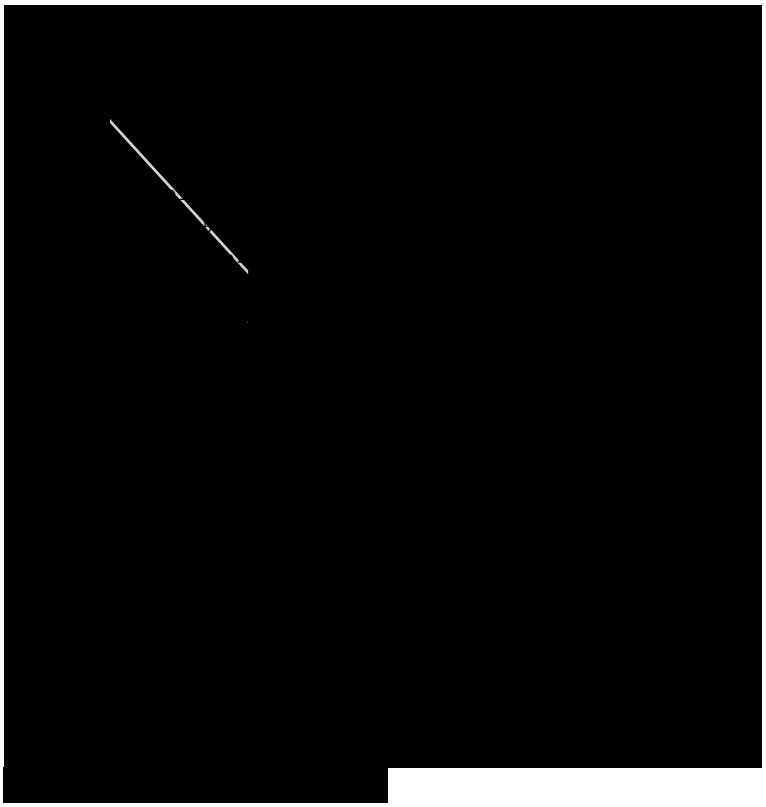
Appendix 9 – Graphical presentation of univariate exploratory analyses (All-cause mortality)

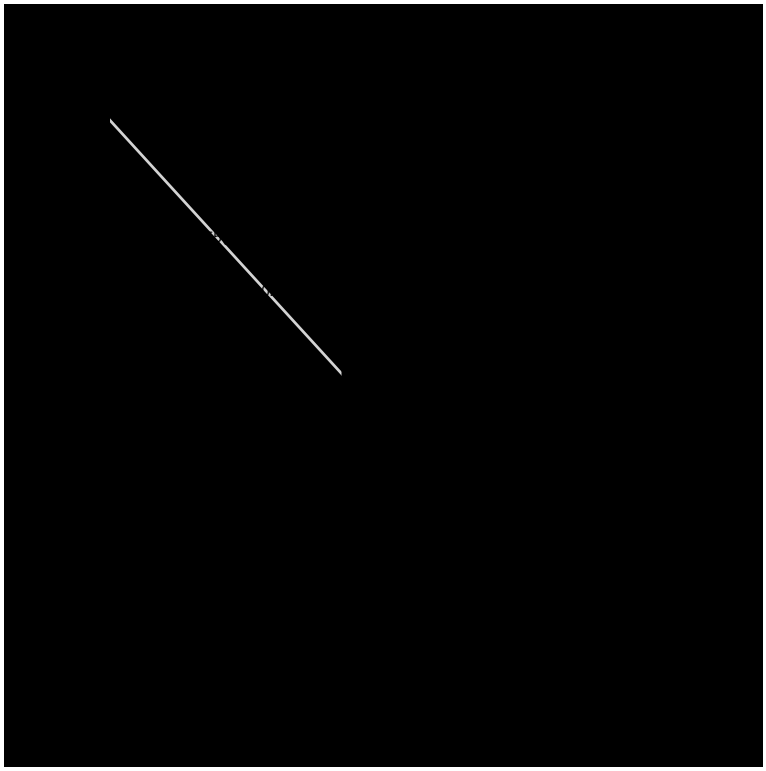
Note: p-values rounded to three decimal places.

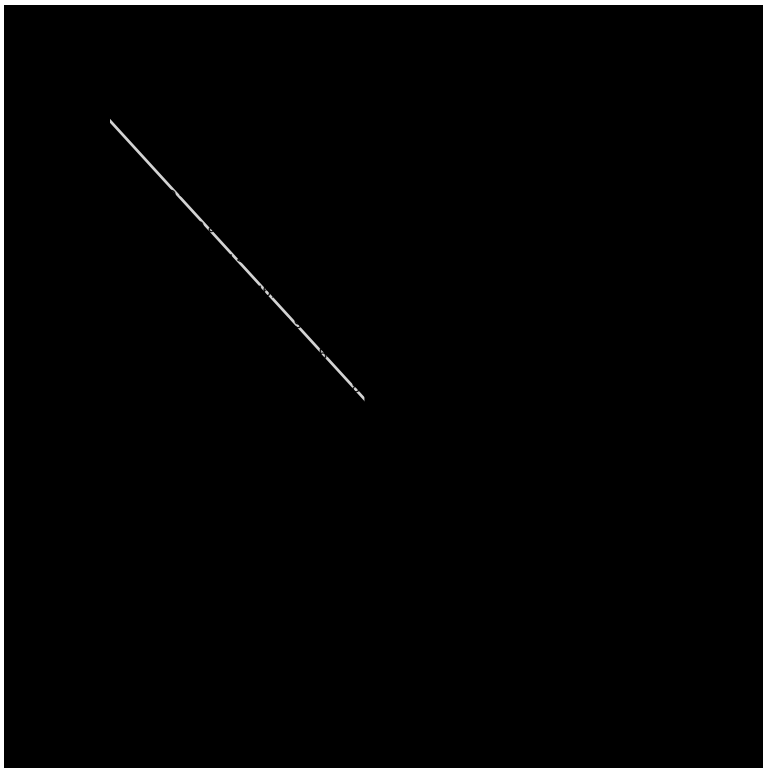


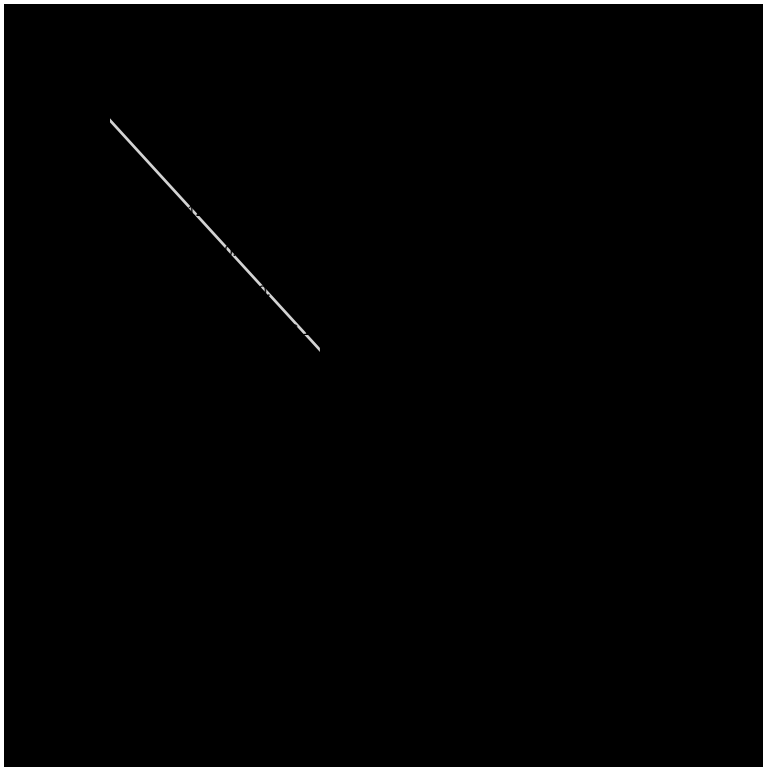


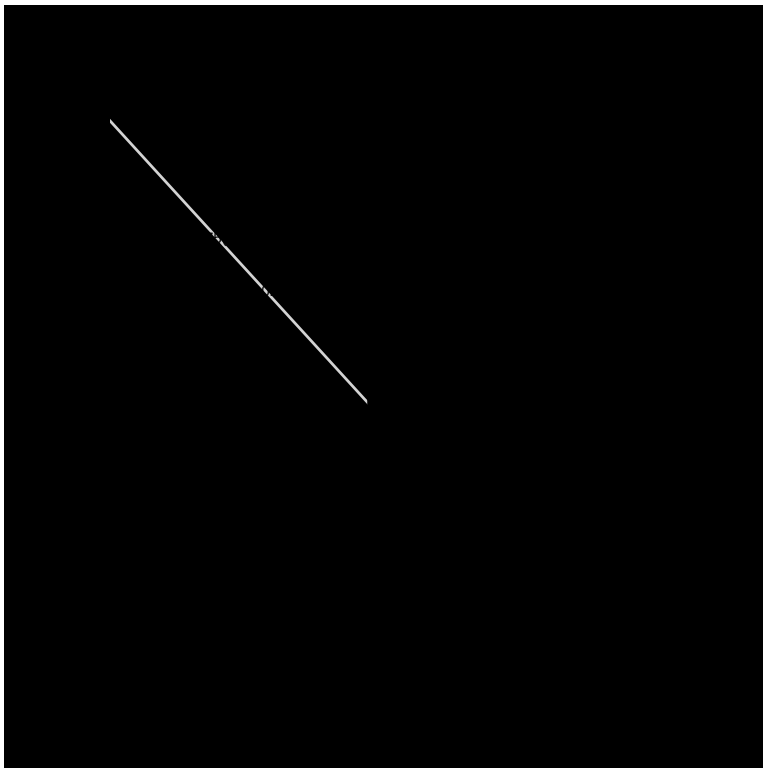












Appendix 10 – Parameters used in sensitivity analysis examining inclusion of NYHA 4 as a treatment effect modifier (all-cause mortality)

Variable[a]	Hazard ratio	P-value
ICD	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]
QRS<120	[redacted]	[redacted]
QRS>=120	[redacted]	[redacted]
LBBB	[redacted]	[redacted]
AGE>=60	[redacted]	[redacted]
GENDER=M	[redacted]	[redacted]
NYHA4	[redacted]	[redacted]
ICD*QRS<120	[redacted]	[redacted]
ICD*QRS>=120	[redacted]	[redacted]
ICD*LBBB	[redacted]	[redacted]
ICD*GENDER=M	[redacted]	[redacted]
ICD*AGE>=60	[redacted]	[redacted]
ICD*NYHA4	[redacted]	[redacted]
CRTP*QRS>=120	[redacted]	[redacted]
CRTP*LBBB	[redacted]	[redacted]
CRTP*GENDER=M	[redacted]	[redacted]
CRTP*AGE>=60	[redacted]	[redacted]
CRTP*NYHA4	[redacted]	[redacted]
CRTD*QRS>=120	[redacted]	[redacted]
CRTD*LBBB	[redacted]	[redacted]
CRTD*GENDER=M	[redacted]	[redacted]
CRTD*AGE>=60	[redacted]	[redacted]
CRTD*NYHA4	[redacted]	[redacted]

Appendix 11: LOS approach to modelling all-cause hospitalisation

Estimation of baseline rate

A similar process to that described in section 4.3 for expected number of events was performed, with the negative binomial model again selected. The same variables were considered as predictors. The final model was again selected using a stepwise approach (P=0.05), and the covariates are presented in Table 24. The plot of observed compared to predicted proportions is presented in Figure 1.

Table 24: NBRM used to predict baseline monthly length of stay (days, OPT)

Covariable	B Coefficient	Std. error	Z score	e^β
NYHA = III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA=IV	[redacted]	[redacted]	[redacted]	[redacted]
Non-North American region	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Comparison of observed vs. fitted baseline length of stay (days, OPT)

[redacted]

The derived monthly values for individuals who are NYHA I/II, III or IV are [redacted] days, respectively. Since the analyses are to be used in a UK clinical context, the non-North American binary variable was set to 1 in all

calculations. The starting age was again assumed to be 66.

The predicted days per month hospitalised for all NYHA classes are small, and so careful consideration as to the appropriateness of these results is required. On the basis of information in the latest NHS schedule of reference costs, the mean length of stay is 3.03 days for all elective procedures and 5.65 days for all non-elective procedures. Restricting the calculation to cardiovascular related procedures, the two values are 2.96 and 4.67 days respectively. Within this category further restriction to heart failure related hospitalisation (currency code EB03) yields weighted average LOS estimates of 6.28 and 7.56 days respectively. Thus, regardless of which category is used, average hospital stays for procedures are short. For the purposes of the current analysis we have used the data for all cardiovascular related admissions in our costing protocols.

Given the low probabilities of being hospitalised in any given month and the expected length of stay for an event, the expected number of days in hospital per month will be very low. The derived values are therefore in line with what would be expected in routine practice.

Estimation of treatment effect on hospital stay

The process for estimating the impact of treatment on the number of days per month spent in hospital was identical to that described for the number of events per month. The preferred model was again the NBRM and the final covariates used, again after removal of all redundant parameters, are presented in Table 25. The comments relating to the modelling of number of events per month are equally relevant here and will not be repeated. In particular, the assumptions made relating to the use of alternative values are assumed to hold for length of stay. Interactions between ischaemic aetiology and treatment option were again included as potential covariates. The derived treatment effects are presented in Table 26

Table 25: Negative binomial model used to predict the impact of treatment on days per month hospitalised

Covariable	β Coefficient	Std. error	Z score	e^β
Device = ICD	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-D and ischaemic	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-P and ischaemic	[redacted]	[redacted]	[redacted]	[redacted]
Device = CRT-P and NYHA = IV	[redacted]	[redacted]	[redacted]	[redacted]

Table 26: Treatment effects on all cause hospitalisation (days per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
ICD	[redacted]	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]	[redacted]
Ischaemicaetiology			
ICD	[redacted]	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]	[redacted]

* IPD analysis counter-intuitive since both treatment options involve common element (CRT). Hence CRT-D value used for both options.

The final values used in the model for this sensitivity analysis are presented in Table 27 to Table 29.

Table 27: All-cause hospitalisation (ICD, days per month)

	NYHA I/II	NYHA III	NYHA IV
Ischaemic aetiology	[redacted]	[redacted]	N/A
Non-ischaemic aetiology	[redacted]	[redacted]	N/A

Table 28: All-cause hospitalisation (CRT-P, days per month)

	NYHA I/II	**NYHA III**	**NYHA IV**
Ischaemic aetiology	N/A	[redacted]	[redacted]
Non-ischaemic aetiology	N/A	[redacted]	[redacted]

Table 29: All-cause hospitalisation (CRT-D, days per month)

	NYHA I/II	**NYHA III**	**NYHA IV**
Ischaemic aetiology	[redacted]	[redacted]	[redacted]
Non-ischaemic aetiology	[redacted]	[redacted]	[redacted]

Appendix 12: Justification for method used to model HRQoL

In addition to Poisson and negative binomial models, zero inflated versions of the two models were also considered, given the very high proportion of patients reporting a value 1 (and hence a change from unity of 0%). Overall, the Zero Inflated Negative Binomial (ZINB) model was the option that best fitted the data on the basis of formal statistical tests (BIC, AIC, Vuong) and assessment of goodness of fit.

The clinical parameters assessed for potential impact on baseline utility were NYHA class, LVEF, ischaemic aetiology, QRS duration and gender. Additional variables considered were geographical location (US, non-US) and baseline age. At the time of analysis stepwise variable selection was not available in combination with ZINB, and so model selection was made via a series of likelihood ratio tests. LVEF was the only variable removed from the full model.

However, close inspection of the final model, in particular the “always zero” component, raised considerable concern. Across the whole data set there were only [redacted] patients with NYHA IV, and only four of these reported a utility score of 1 (i.e. a decrement of zero). Hence, the ZINB model was extremely unstable and appeared not to have converged despite running for 5,000 iterations. The lack of convergence would have meant that a probabilistic sensitivity analysis would not have been possible, as a Cholesky decomposition matrix could not be constructed. The derived results from the model were also counter-intuitive in that patients with a very wide QRS were predicted to have a better HRQoL than patients who had a narrower QRS. Overall, despite being technically the most appropriate model, the ZINB model was not used in the final analysis, and instead the second best fit – a negative binomial model – was used.

APPENDIX 13: Cost-effectiveness frontiers for all patient groups

In order to provide the committee with the greatest amount of information, we have produced and presented the information in Table 11 and Table 12 (main report section 6.1) as cost-effectiveness frontiers. For convenience, these are grouped by LBBB status and NYHA class. Note that all discussion in relation to the patient count in each group is also applicable to the interpretation of these plots.

No LBBB, NYHA I

Figure 2: Cost-effectiveness frontier (NYHA I, QRS<120ms, non-ischemic, no LBBB)

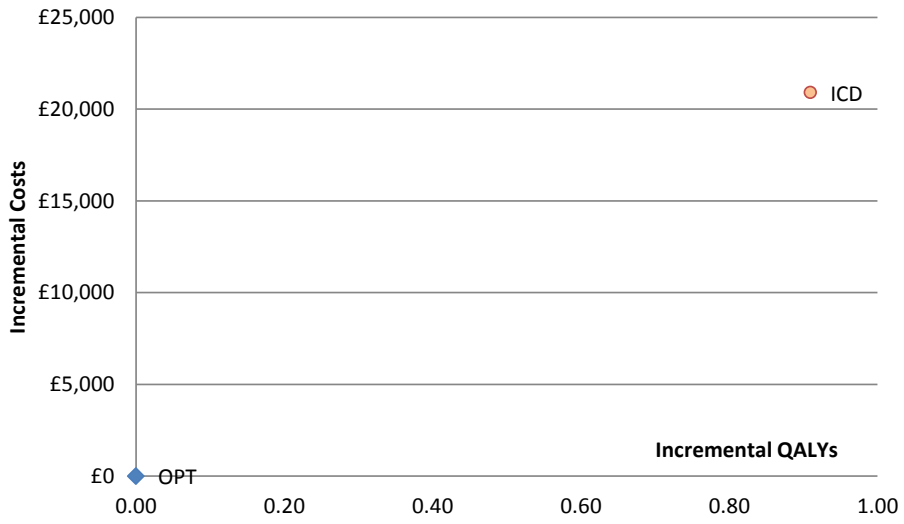


Figure 3: Cost-effectiveness frontier (NYHA I, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

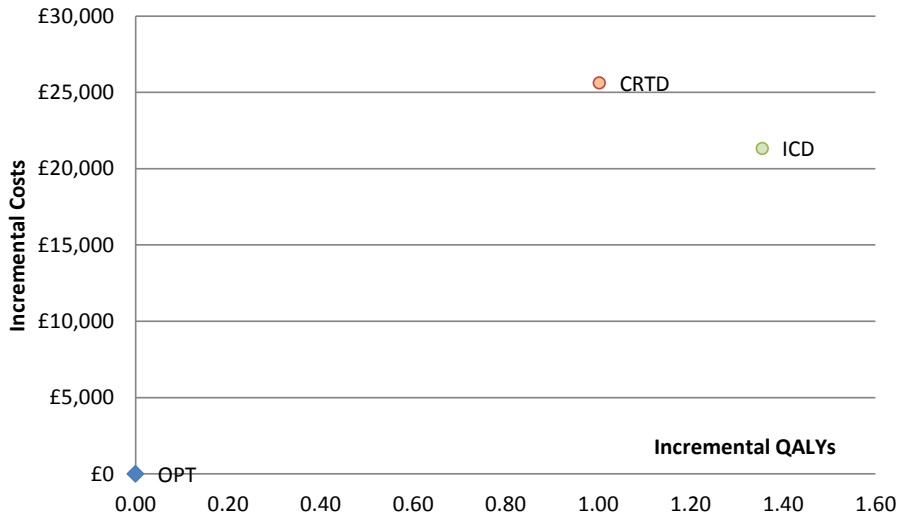


Figure 4: Cost-effectiveness frontier (NYHA I, QRS≥150ms non-ischemic, no LBBB)

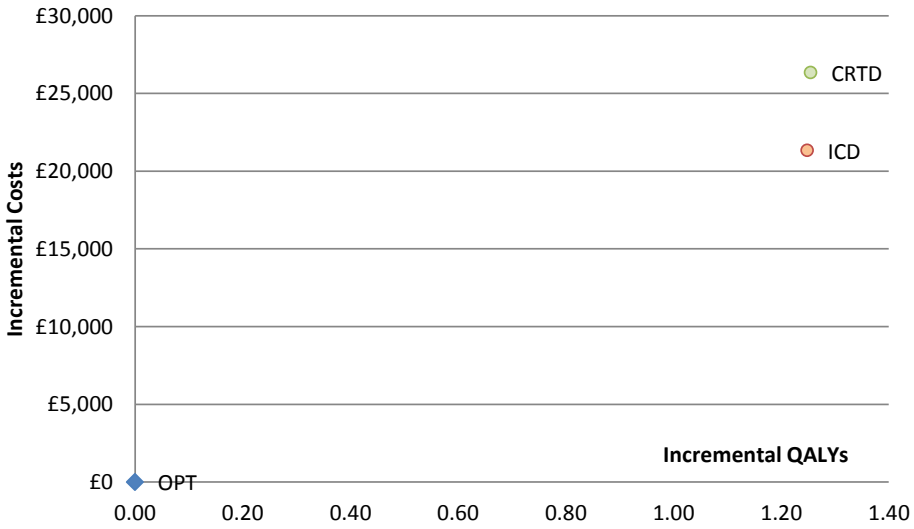


Figure 5: Cost-effectiveness frontier (NYHA I, QRS<120ms, ischemic, no LBBB)

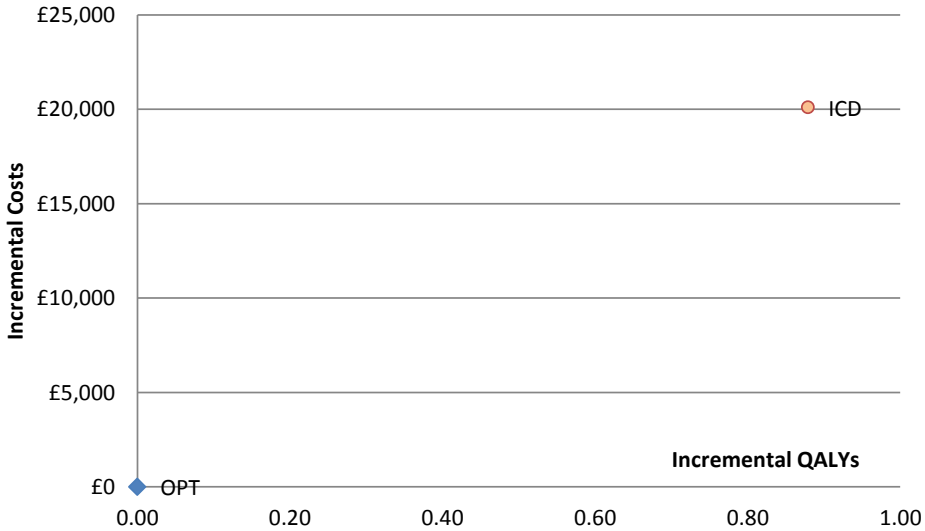


Figure 6: Cost-effectiveness frontier (NYHA I, QRS≥120ms, ≤149ms, ischemic, no LBBB)

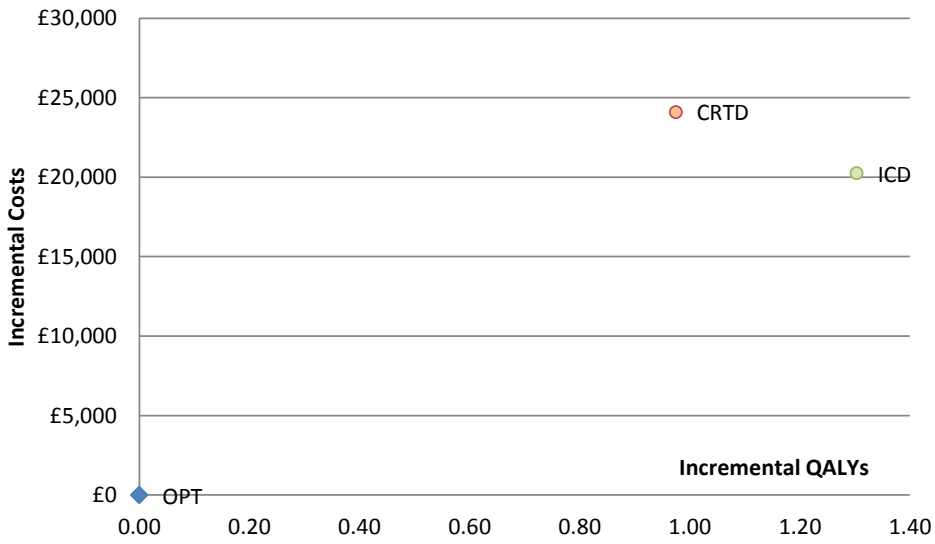
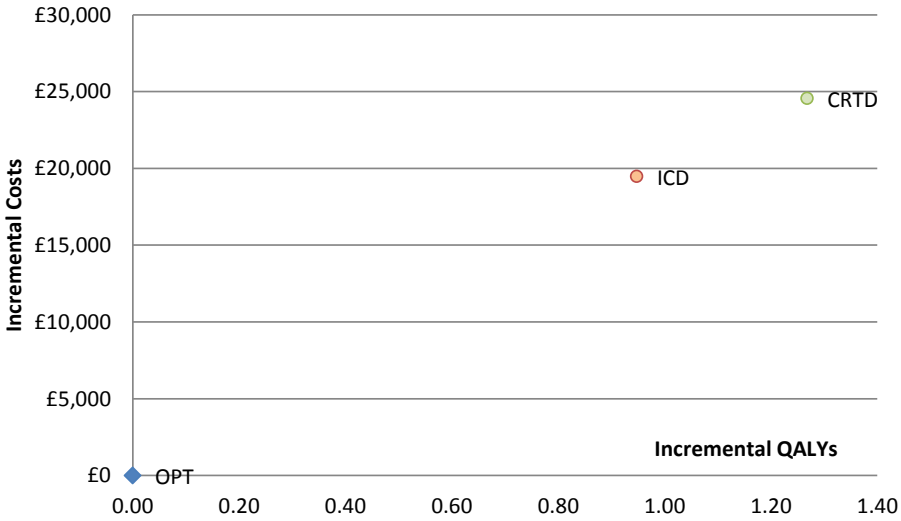


Figure 7: Cost-effectiveness frontier (NYHA I, QRS≥150ms ischemic, no LBBB)



No LBBB, NYHA II

Figure 8: Cost-effectiveness frontier (NYHA II, QRS<120ms, non-ischemic, no LBBB)

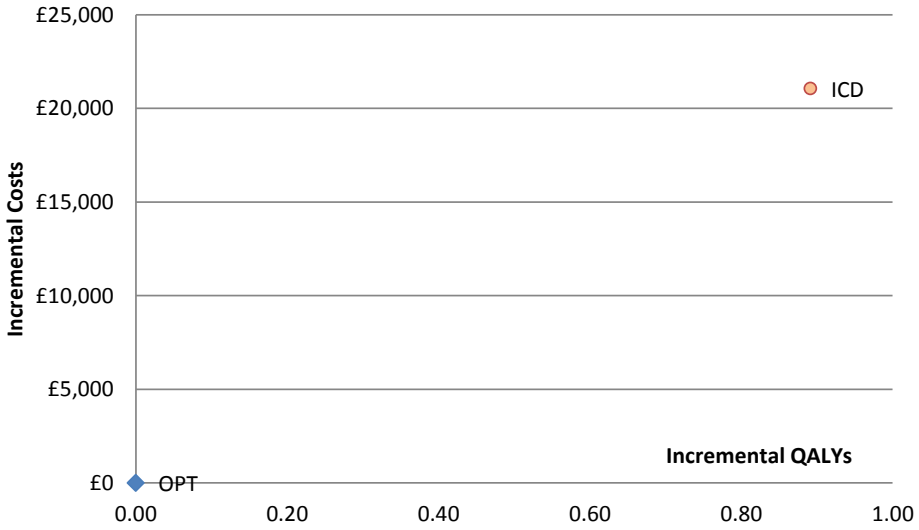


Figure 9: Cost-effectiveness frontier (NYHA II, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

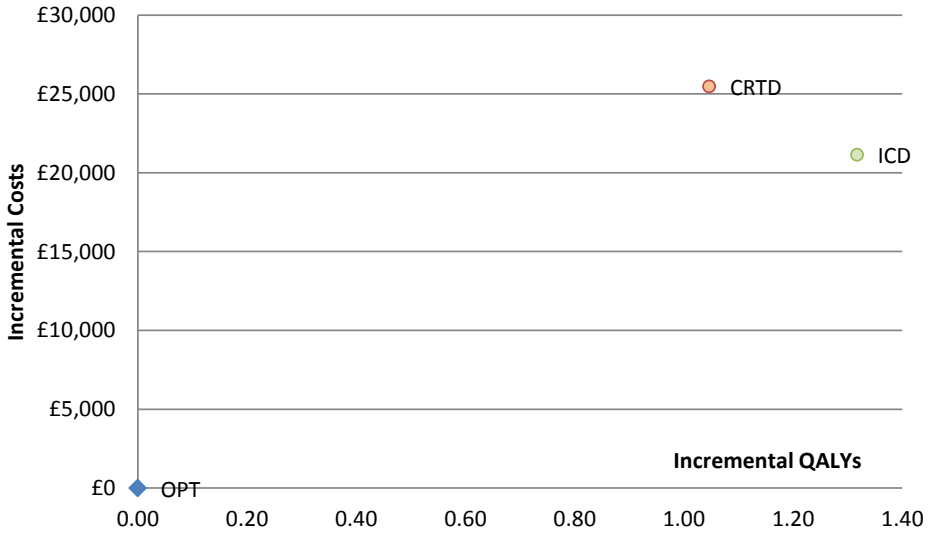


Figure 10: Cost-effectiveness frontier (NYHA II, QRS≥150ms non-ischemic, no LBBB)

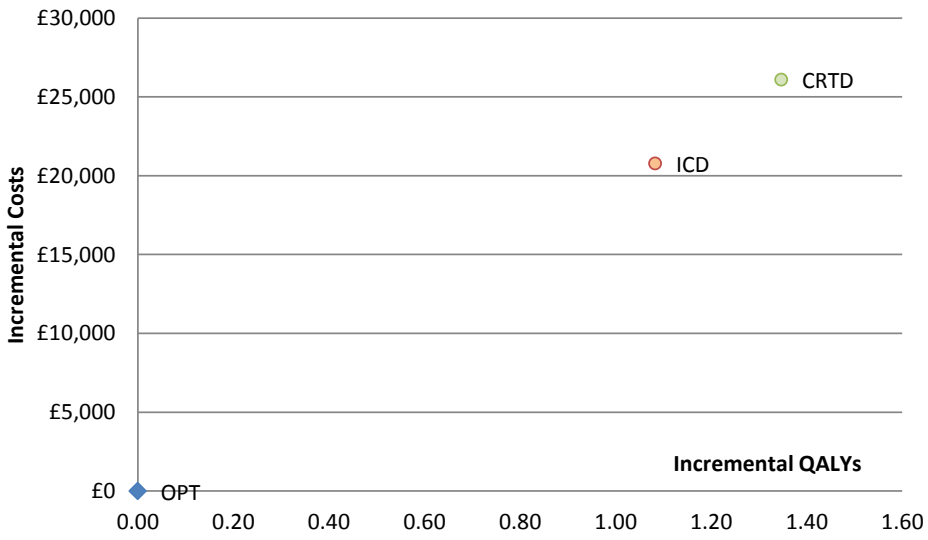


Figure 11: Cost-effectiveness frontier (NYHA II, QRS<120ms, ischemic, no LBBB)

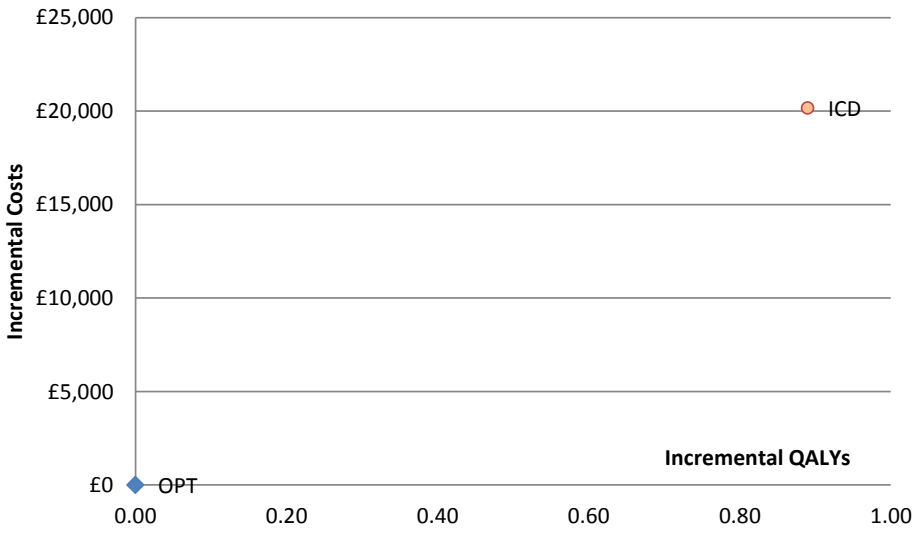


Figure 12: Cost-effectiveness frontier (NYHA II, QRS≥120ms, ≤149ms, ischemic, no LBBB)

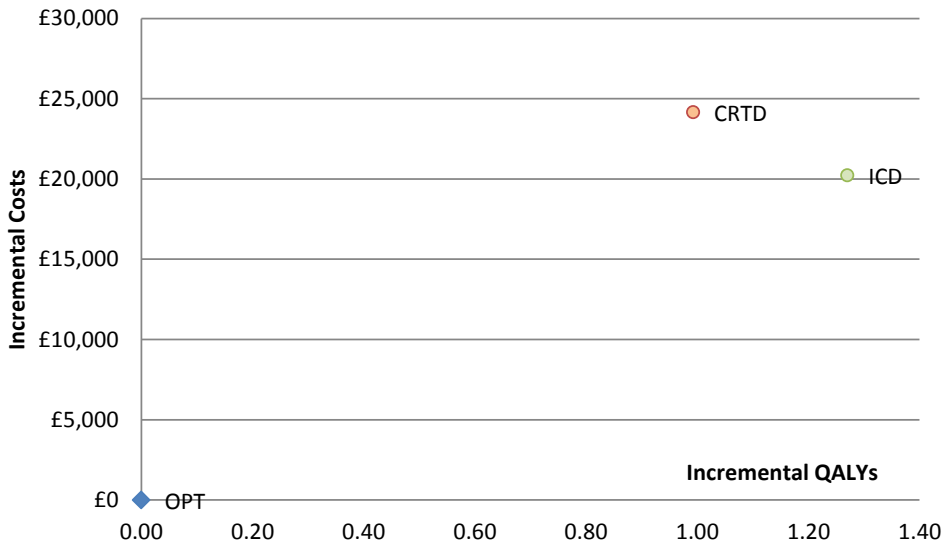
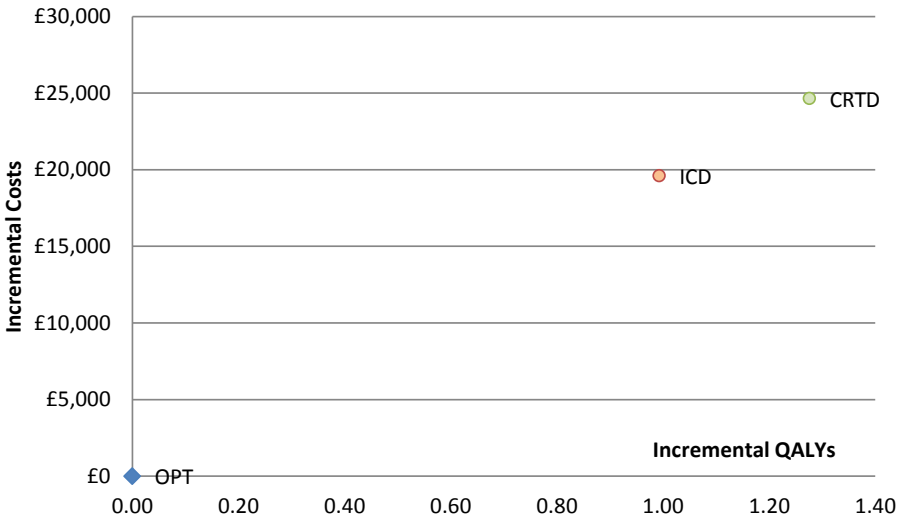


Figure 13: Cost-effectiveness frontier (NYHA II, QRS≥150ms ischemic, no LBBB)



No LBBB, NYHA III

Figure 14: Cost-effectiveness frontier (NYHA III, QRS<120ms, non-ischemic, no LBBB)

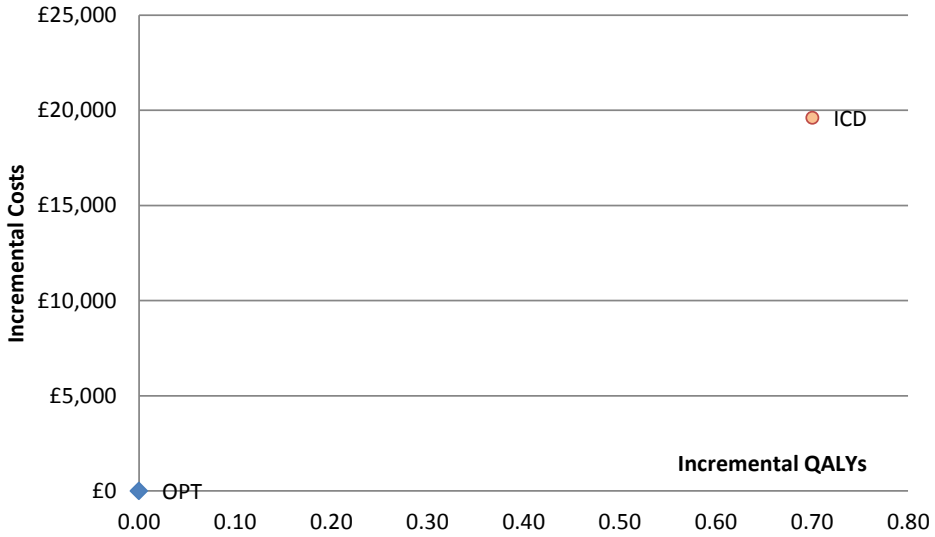


Figure 15: Cost-effectiveness frontier (NYHA III, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

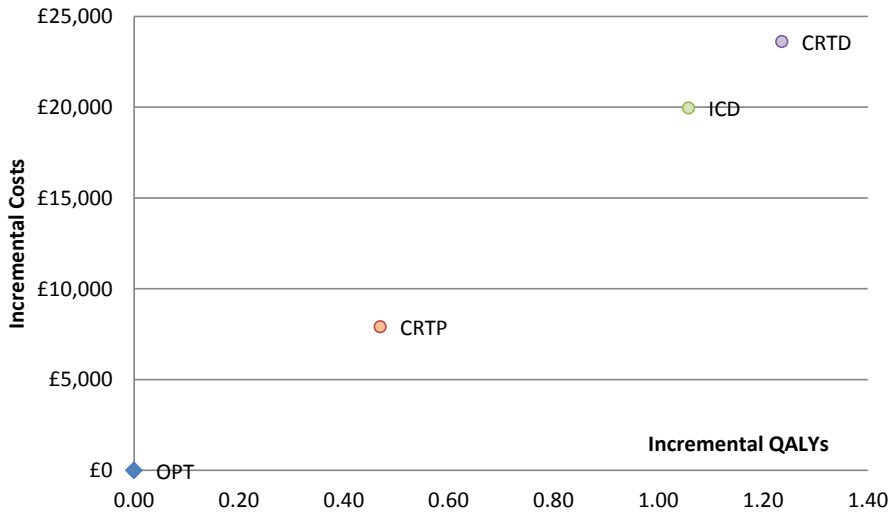


Figure 16: Cost-effectiveness frontier (NYHA III, QRS≥150ms non-ischemic, no LBBB)

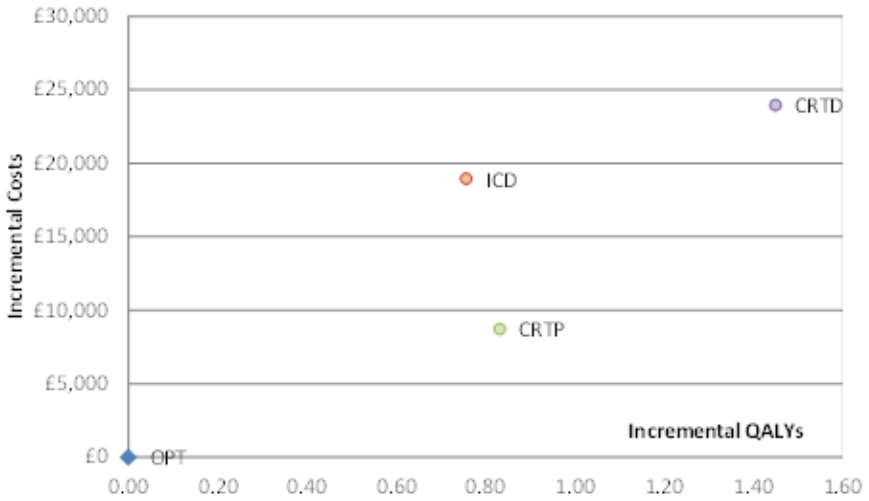


Figure 17: Cost-effectiveness frontier (NYHA III, QRS<120ms, ischemic, no LBBB)

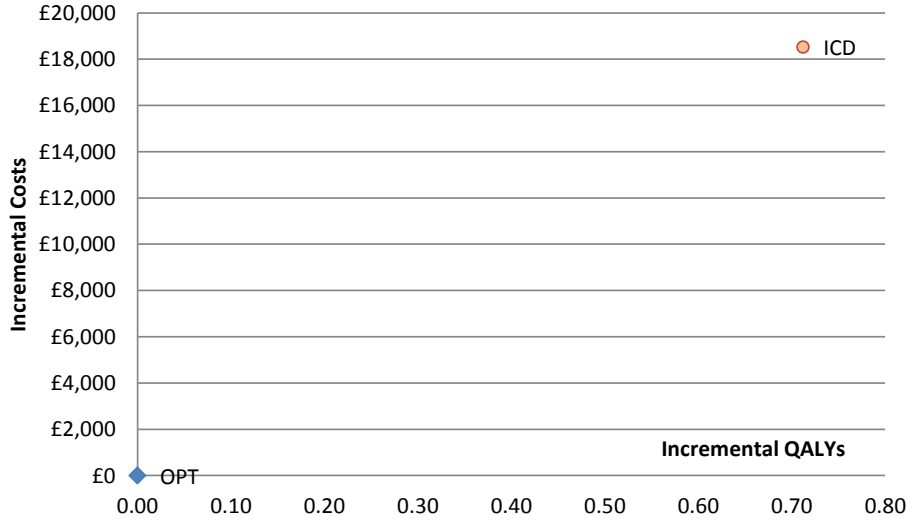


Figure 18: Cost-effectiveness frontier (NYHA III, QRS≥120ms, ≤149ms, ischemic, no LBBB)

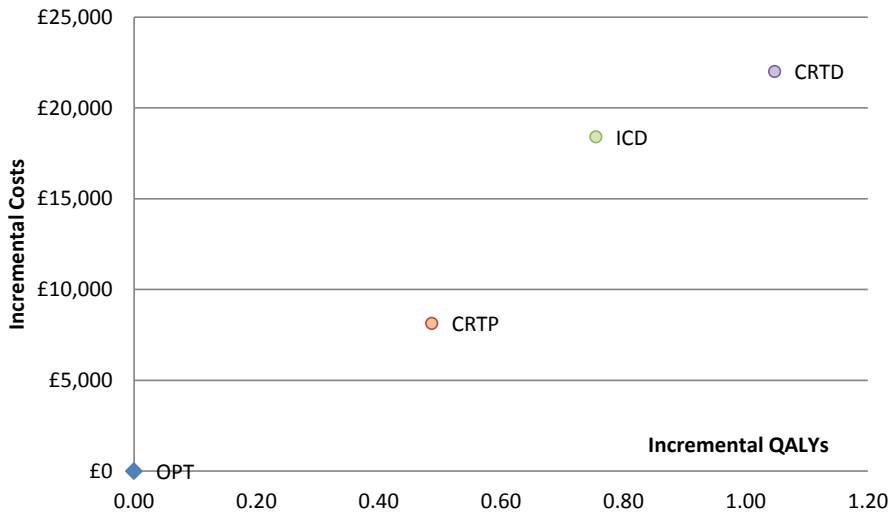
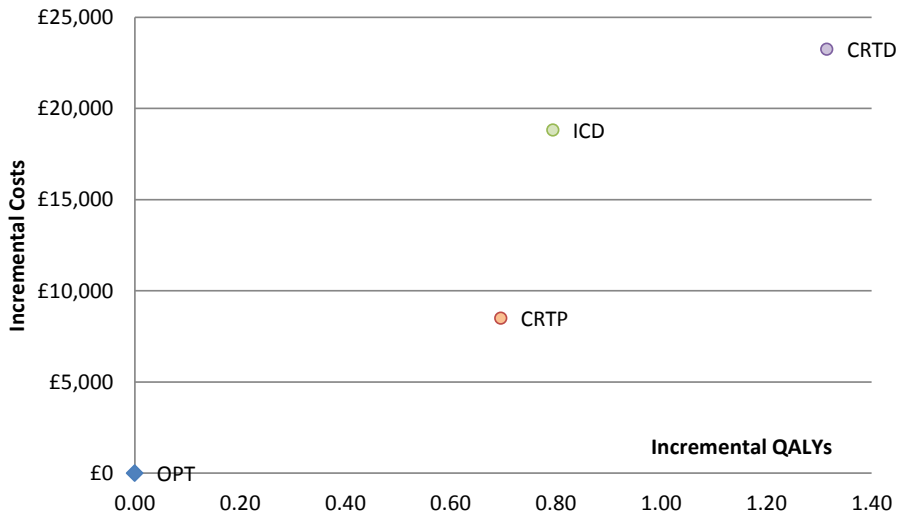


Figure 19: Cost-effectiveness frontier (NYHA III, QRS≥150ms ischemic, no LBBB)



No LBBB, NYHA IV

Figure 20: Cost-effectiveness frontier (NYHA IV, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

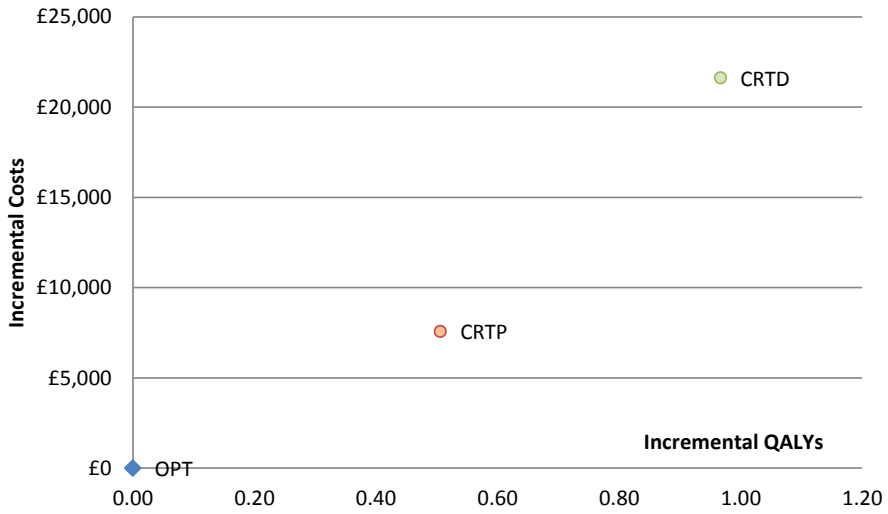


Figure 21: Cost-effectiveness frontier (NYHA IV, QRS≥150ms non-ischemic, no LBBB)

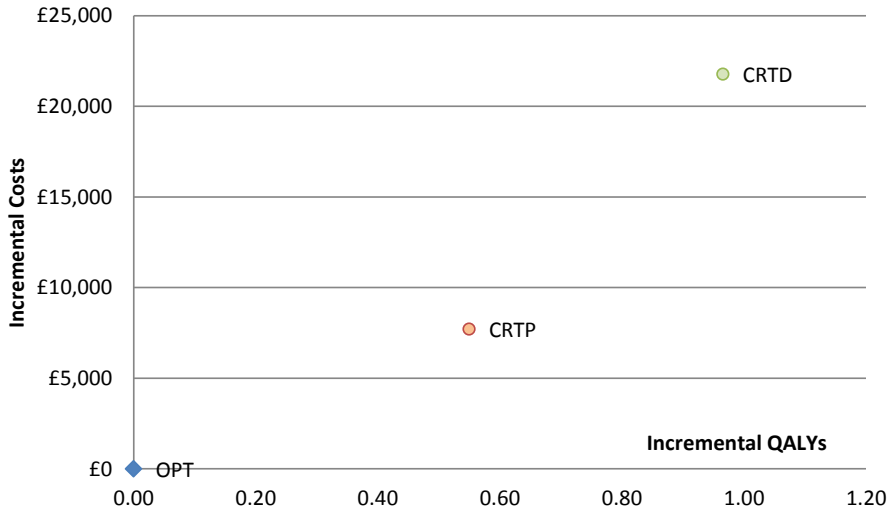


Figure 22: Cost-effectiveness frontier (NYHA IV, QRS≥120ms, ≤149ms, ischemic, no LBBB)

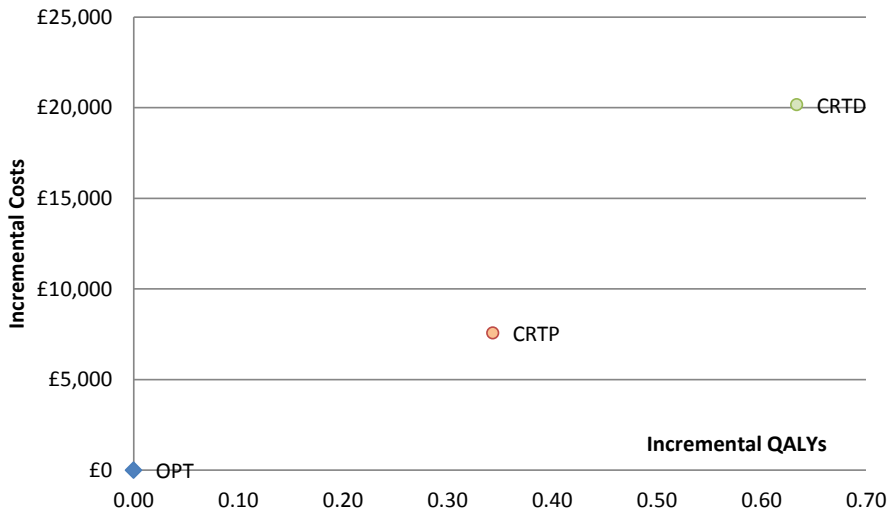
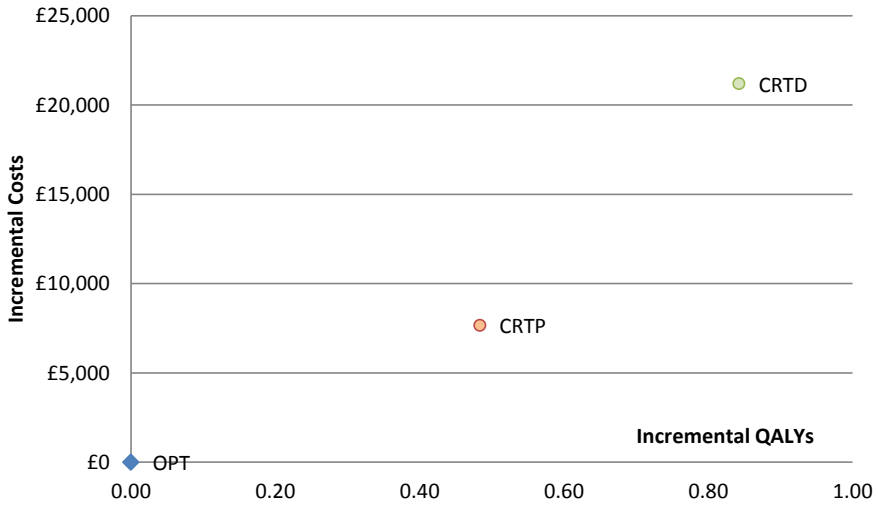


Figure 23: Cost-effectiveness frontier (NYHA I, QRS ≥150ms ischemic, no LBBB)



LBBB, NYHA I

Figure 24: Cost-effectiveness frontier (NYHA I, QRS≥120ms, ≤149ms, non-ischemic LBBB)

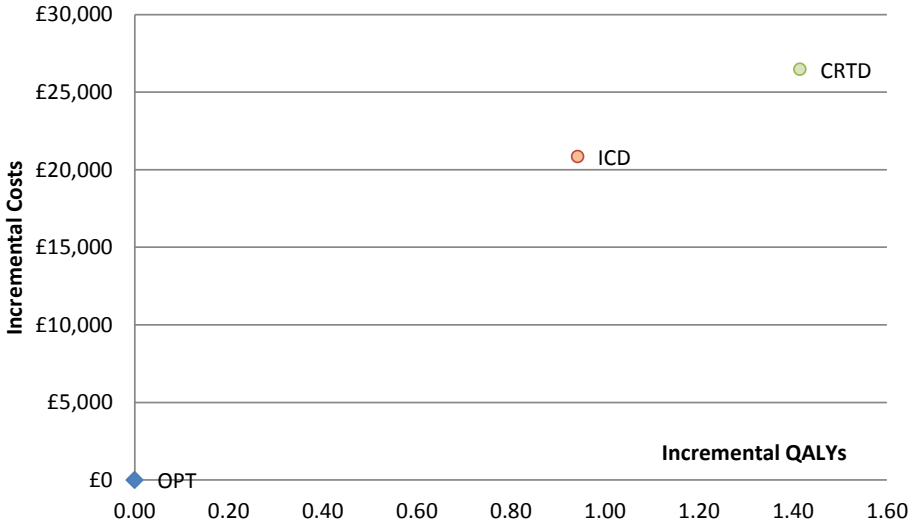


Figure 25: Cost-effectiveness frontier (NYHA I, QRS≥150ms non-ischemic, LBBB)

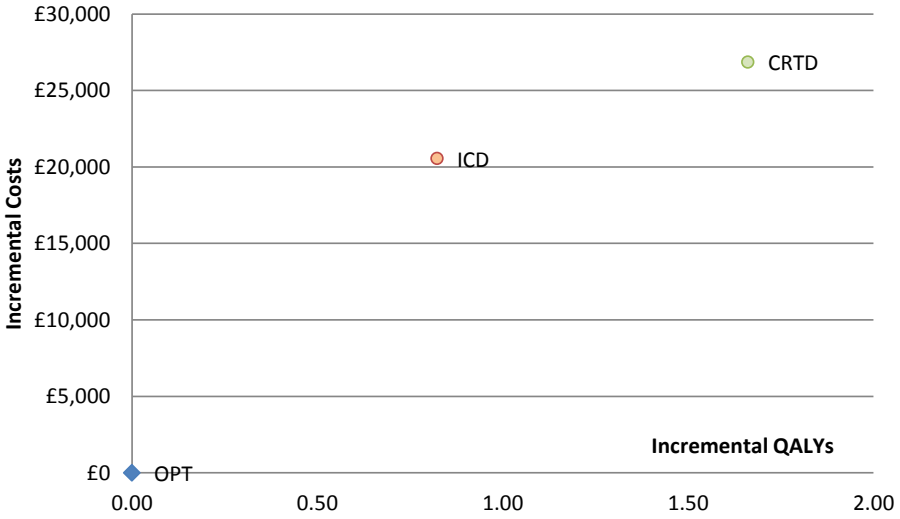


Figure 26: Cost-effectiveness frontier (NYHA I, QRS≥120ms, ≤149ms, ischemic, LBBB)

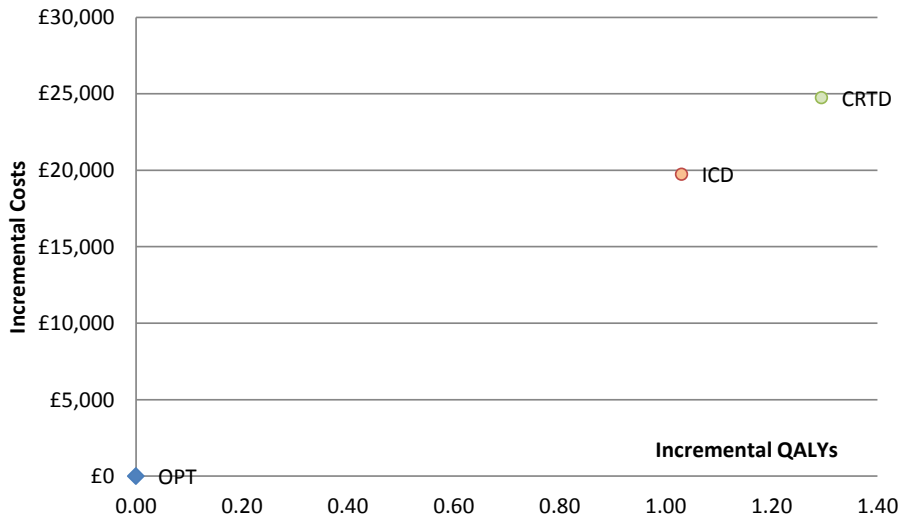
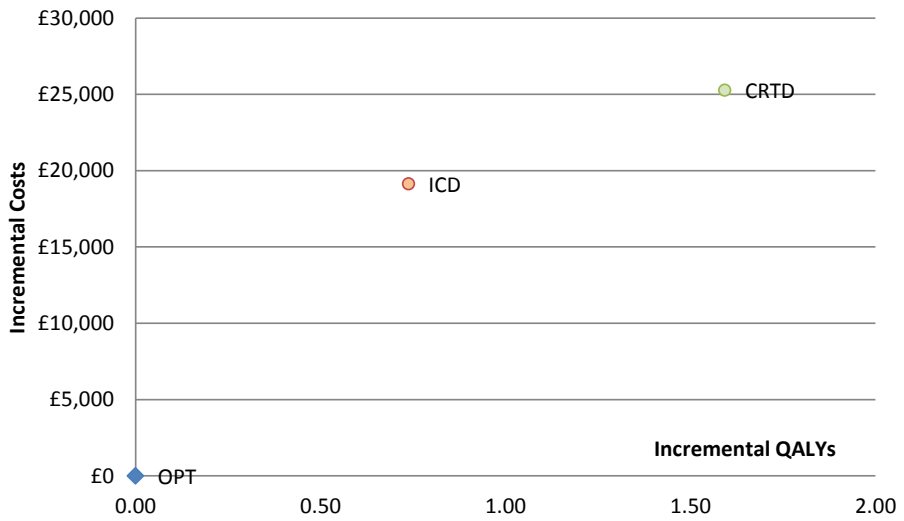


Figure 27: Cost-effectiveness frontier (NYHA I, QRS≥150ms ischemic, LBBB)



LBBB, NYHA II

Figure 28: Cost-effectiveness frontier (NYHA II, QRS≥120ms, ≤149ms, non-ischemic LBBB)

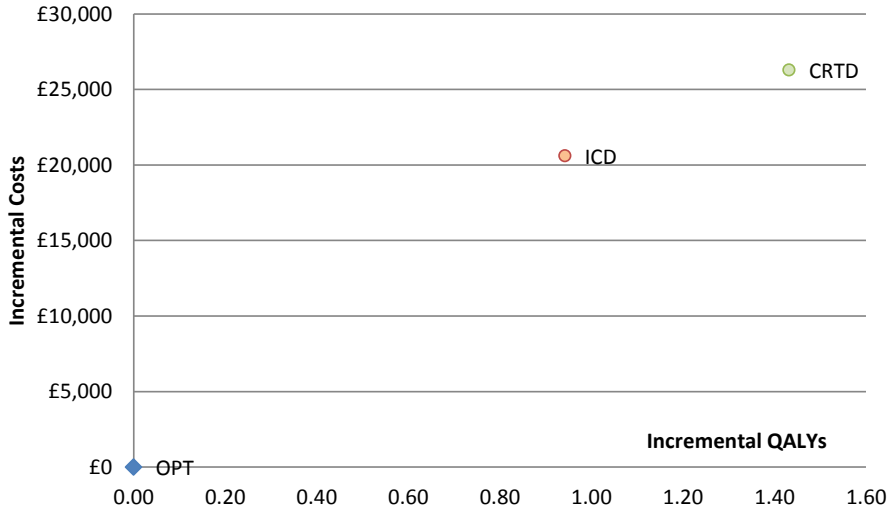


Figure 29: Cost-effectiveness frontier (NYHA II, QRS≥150ms non-ischemic, LBBB)

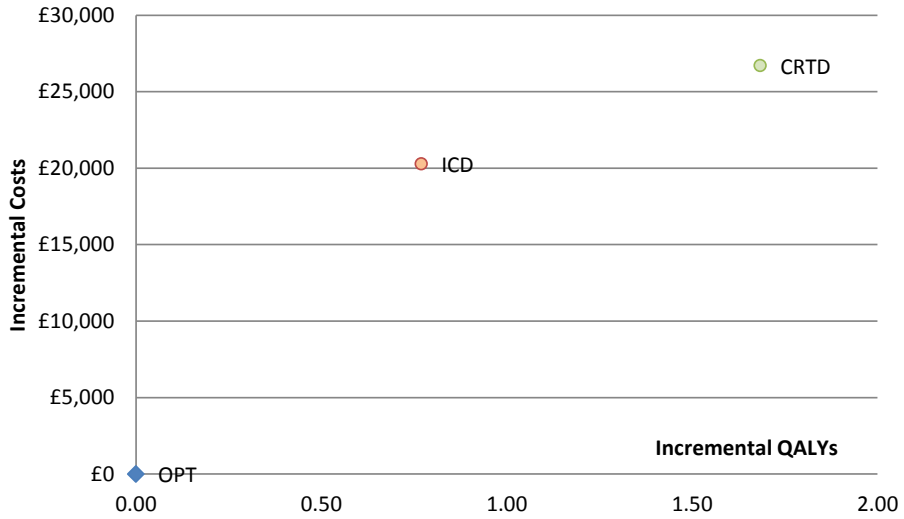


Figure 30: Cost-effectiveness frontier (NYHA II, QRS≥120ms, ≤149ms, ischemic, LBBB)

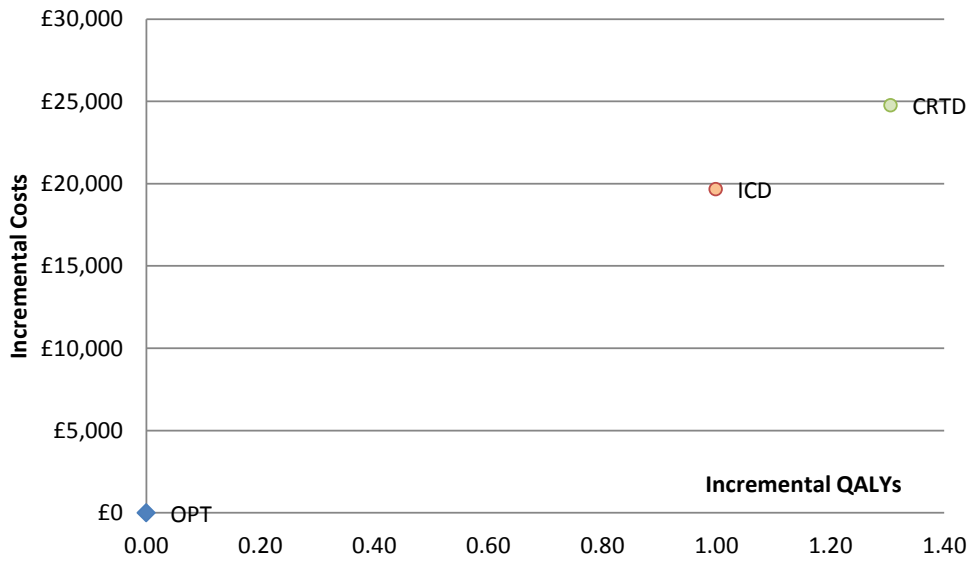
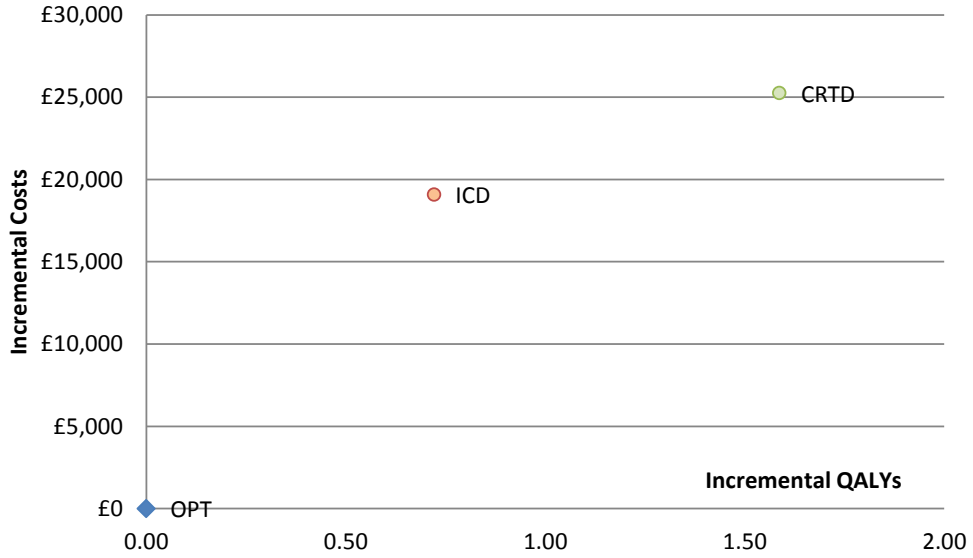


Figure 31: Cost-effectiveness frontier (NYHA II, QRS≥150ms ischemic, LBBB)



LBBB, NYHA III

Figure 32: Cost-effectiveness frontier (NYHA III, QRS≥120ms, ≤149ms, non-ischemic LBBB)

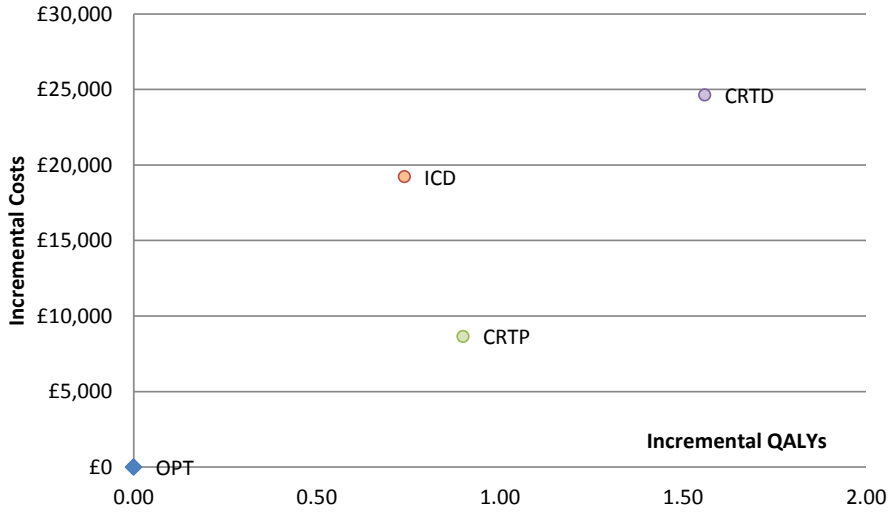


Figure 33: Cost-effectiveness frontier (NYHA III, QRS≥150ms non-ischemic, LBBB)

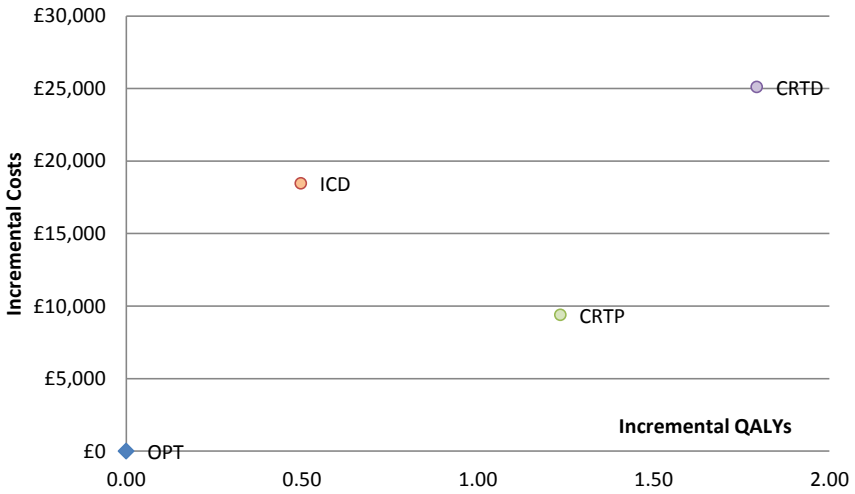


Figure 34: Cost-effectiveness frontier (NYHA III, QRS≥120ms, ≤149ms, ischemic, LBBB)

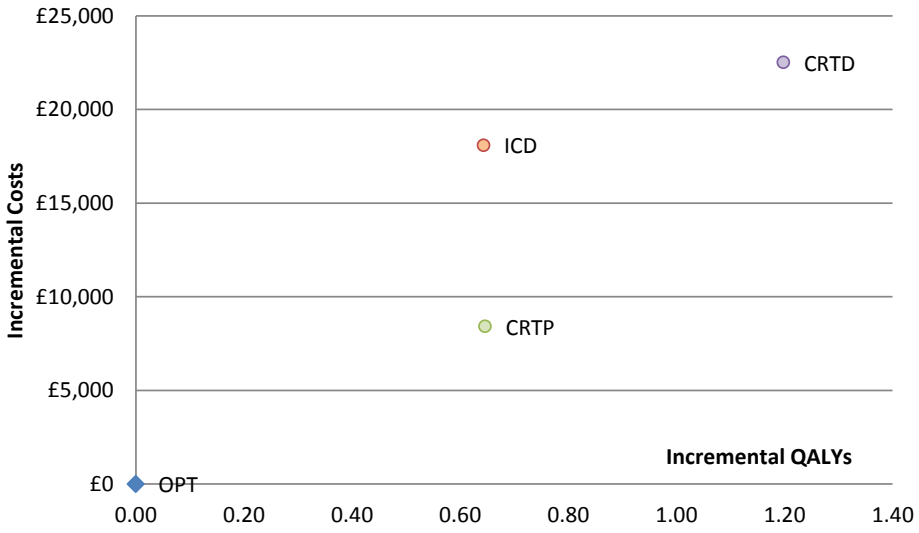
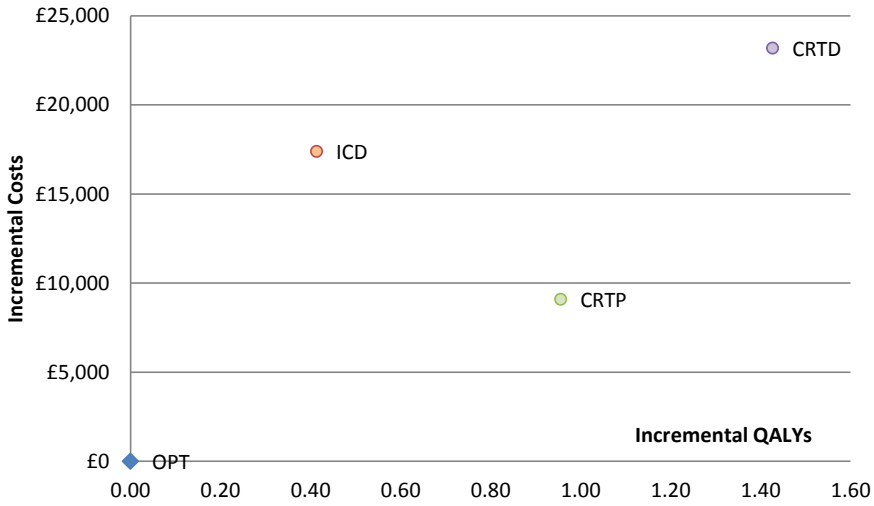


Figure 35: Cost-effectiveness frontier (NYHA III, QRS≥150ms ischemic, LBBB)



LBBB, NYHA IV

Figure 36: Cost-effectiveness frontier (NYHA IV, QRS≥120ms, ≤149ms, non-ischemic LBBB)

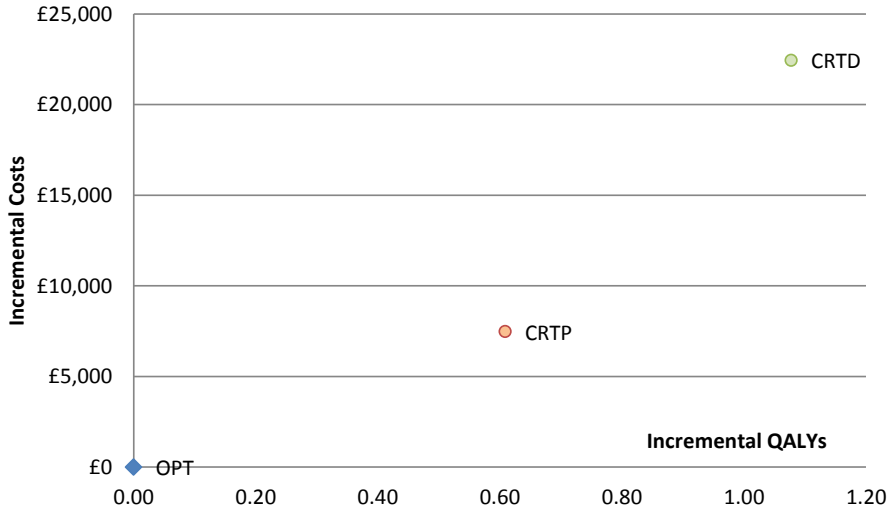


Figure 37: Cost-effectiveness frontier (NYHA IV, QRS≥150ms non-ischemic, LBBB)

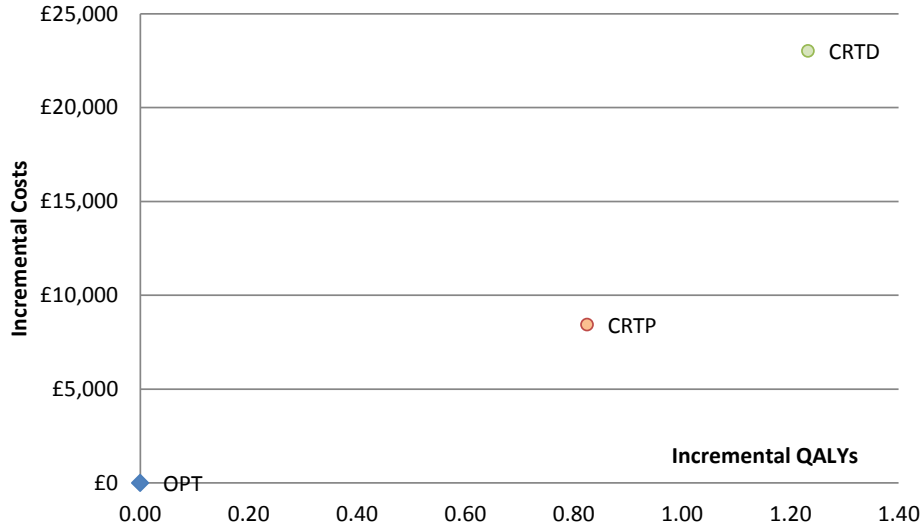


Figure 38: Cost-effectiveness frontier (NYHA IV, QRS≥120ms, ≤149ms, ischemic, LBBB)

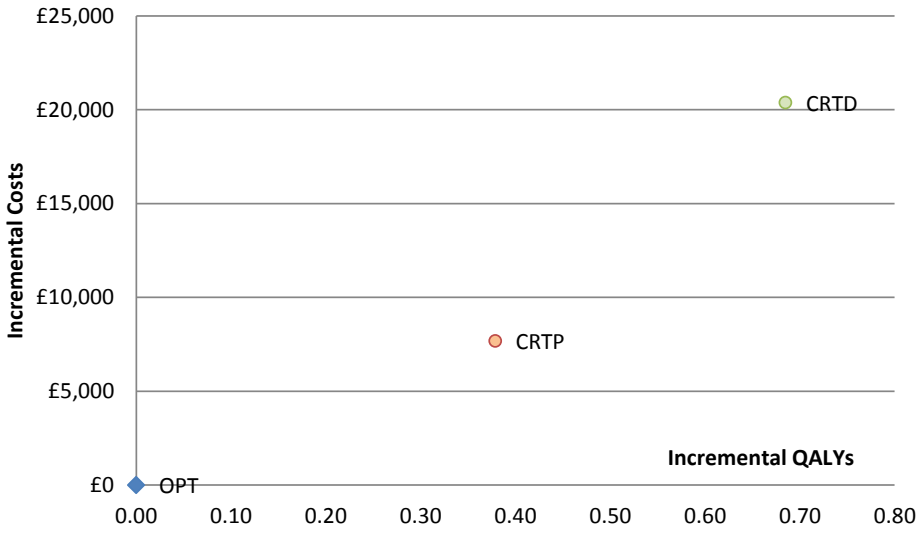
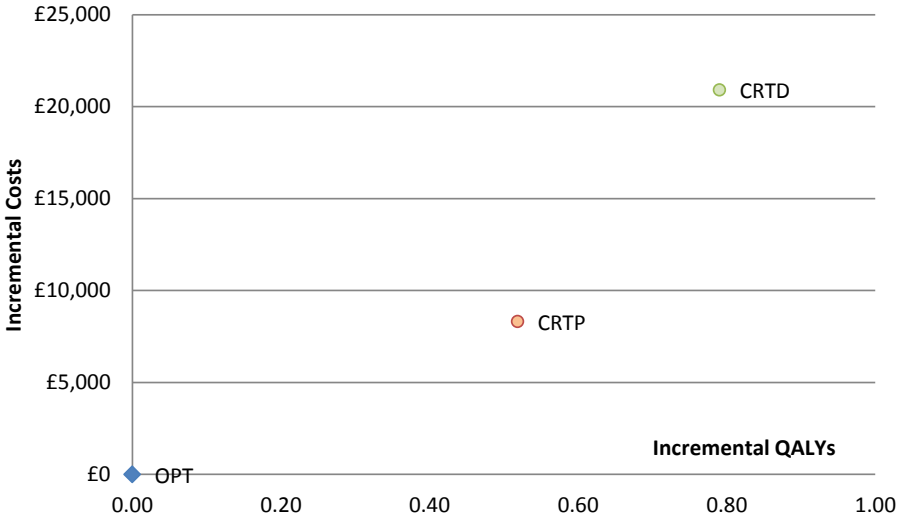


Figure 39: Cost-effectiveness frontier (NYHA IV, QRS≥150ms ischemic, LBBB)



APPENDIX 14: Cost-effectiveness frontiers for all NYHA III patient groups (excluding CRT-P)

Figure 40: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥120ms, ≤149ms, non-ischemic)

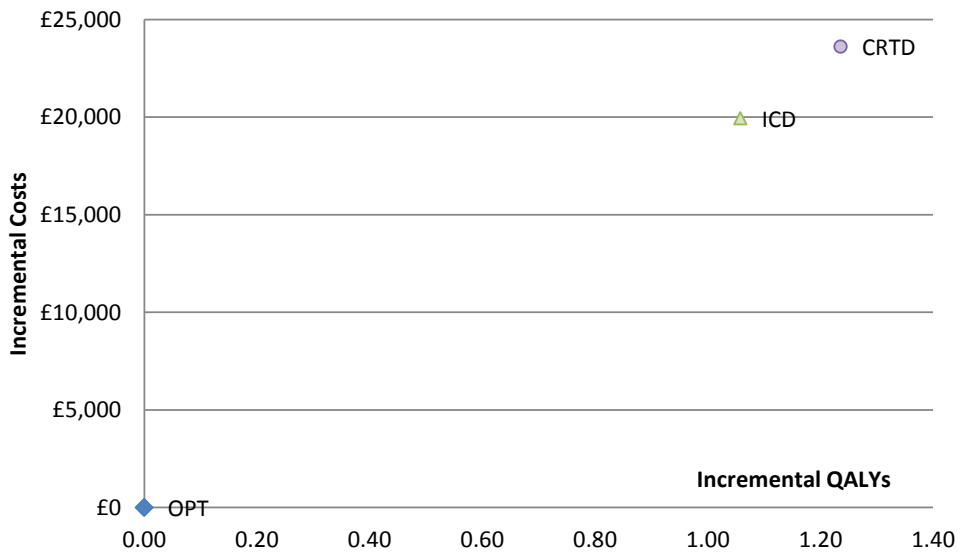


Figure 41: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥150ms, non-ischemic)

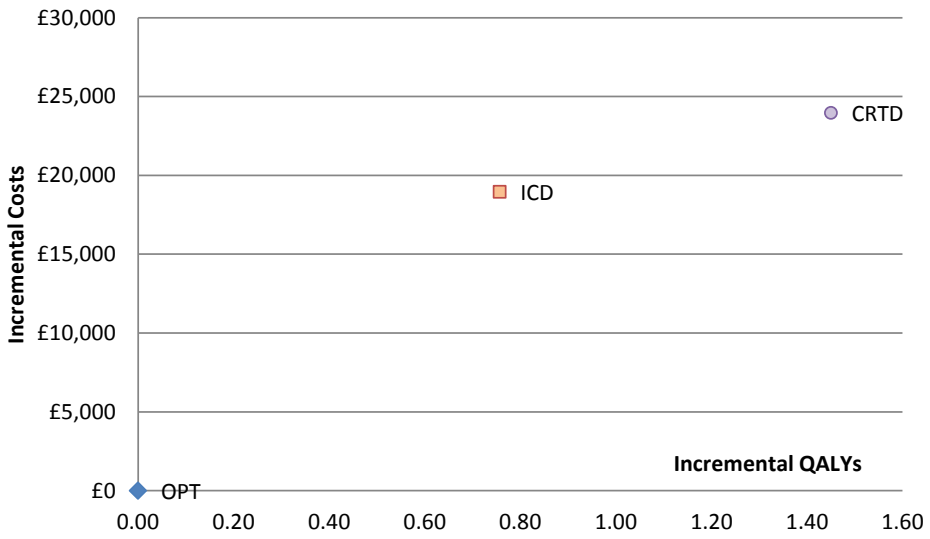


Figure 42: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥120ms, ≤149ms, ischemic)

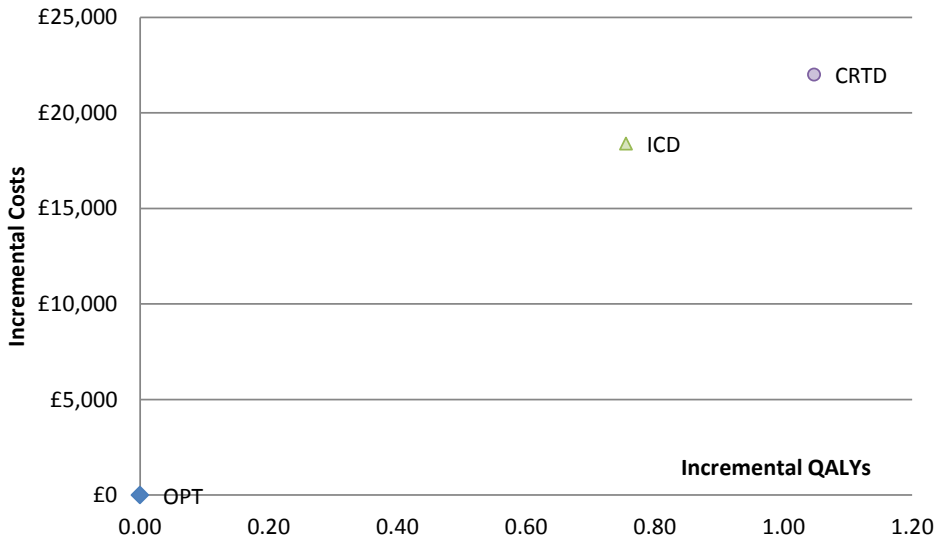


Figure 43: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥150ms, Ischemic)

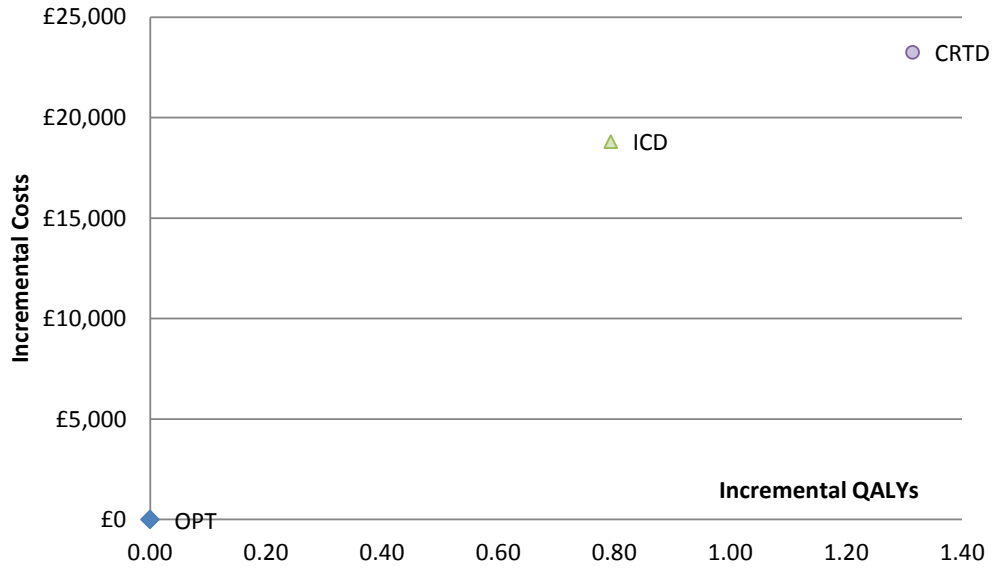


Figure 44: Cost-effectiveness frontier excluding CRT-P (LBBB, QRS ≥120ms, ≤149ms, non-ischemic)

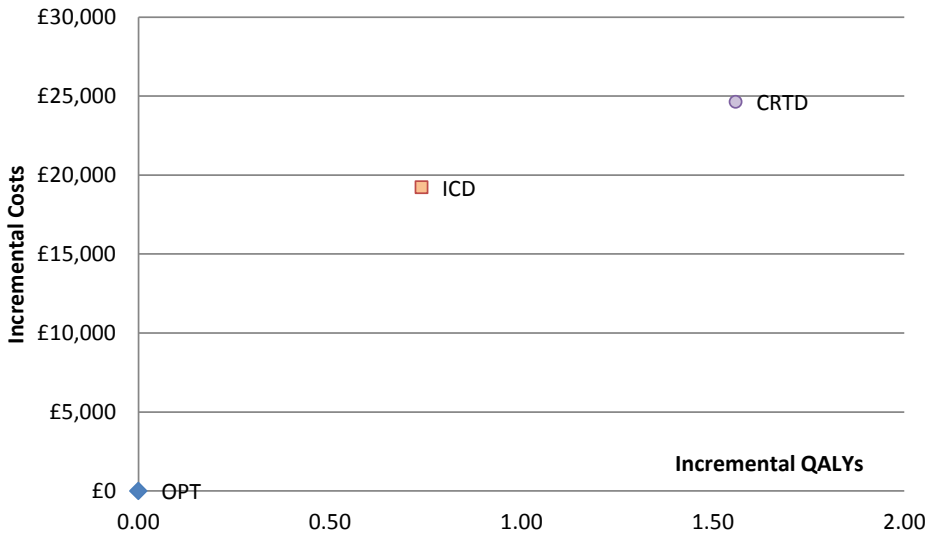


Figure 45: Cost-effectiveness frontier excluding CRT-P (LBBB, QRS ≥150ms, non-ischemic)

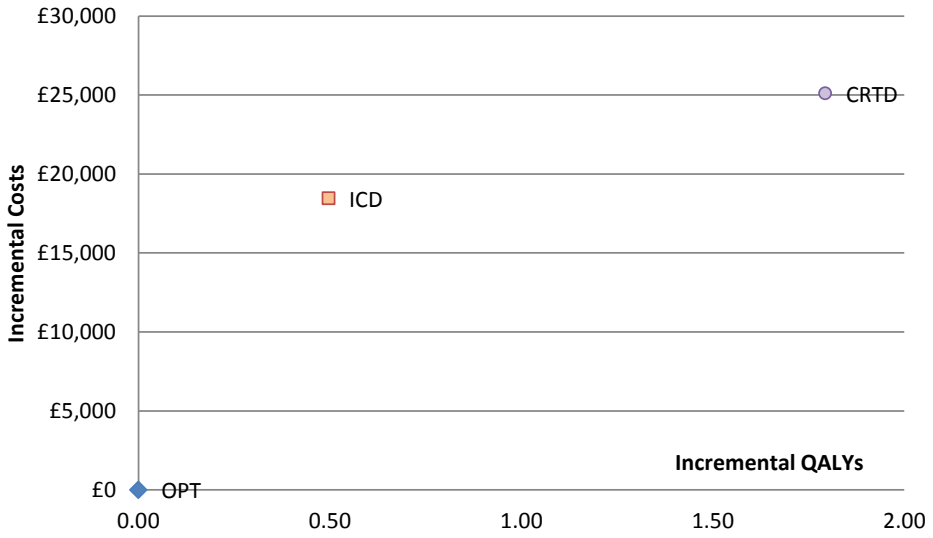


Figure 46: Cost-effectiveness frontier excluding CRT-P (LBBB, QRS ≥120ms, ≤149ms, ischemic)

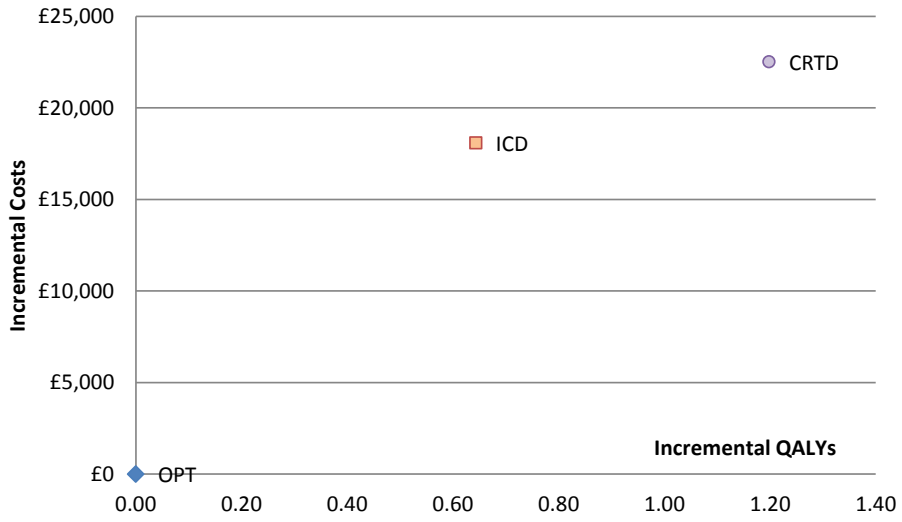
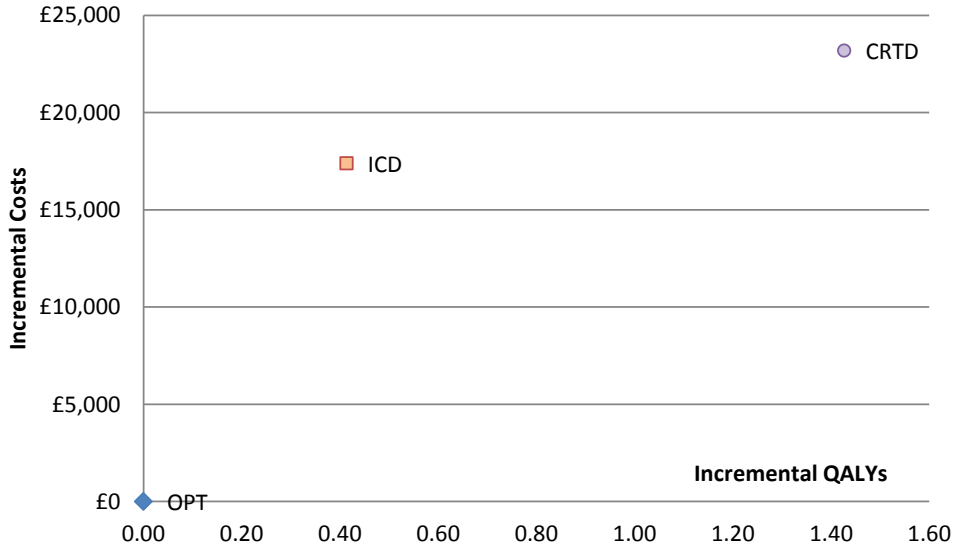


Figure 47: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥150ms, Ischemic)



APPENDIX 15: Additional deterministic sensitivity analyses

Use of length of stay as opposed to event counts to model hospitalisations

As noted in section 4.7, we evaluated the impact of all-cause hospitalisation using a length of stay as well as a count per month approach. The impact of running the model using the LOS method is presented in Table 30 and Table 31. In general, the effect on the ICERs was very modest.

Table 30: Deterministic sensitivity analysis – LOS approach to modelling all cause hospitalisation (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,148	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,030	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,371	£1,201,871	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,076	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,878	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,123	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,840	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,460	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,534	£30,333	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,938	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,370	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,140	£20,344	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,681	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£18,759	£33,621
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£16,258	£21,006
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,748	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£15,653	Ext Dominated	£24,875
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,425	£25,778
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£12,960	£37,818	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£8,698	£41,991	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£11,737	£51,506	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£6,631	£46,232	N/A

Table 31: Deterministic sensitivity analysis – LOS approach to modelling all cause hospitalisation (no LBBB)

NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,030	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,166	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,452	£21,734	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,598	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,658	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,879	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,840	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,751	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£15,856	£20,109
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,662	£22,966
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,655	£25,546
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,838	£29,884
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£11,159	£39,589	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£10,114	£44,980	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£11,560	£49,124	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£10,305	£55,748	N/A

Increase in period of mortality treatment effect

As noted in section 3.9, long term evidence supports the possibility that the benefits of treatment in terms of reduction in all-cause mortality last longer than we have included in the base case. We have therefore explored the impact of maintaining the treatment effect for 10 years instead of 7.5 years on the cost-effectiveness of all devices. The results are presented in Table 32 and Table 33.

As expected, the impact of the change is more pronounced in patients with NYHA I/II heart failure than in those with NYHA III/IV heart failure. Increasing the period of treatment benefit has, in general, reduced all ICERs, but the changes are fairly modest. Hence, the model is insensitive to increases in this parameter.

Table 32: Deterministic sensitivity analysis – mortality treatment effect maintained for ten years (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,902	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,644	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,000	£1,675,069	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,851	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,504	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,215	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,668	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,079	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,206	£25,787	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,722	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,008	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,853	£21,764	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£28,008	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£18,916	£29,969
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,025	£23,330
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,152	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,572	Ext Dominated	£24,252
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,254	£24,904
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£17,254	£30,154	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£16,227	£33,282	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£24,335	£43,180	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£18,008	£37,297	N/A

Table 33: Deterministic sensitivity analysis – mortality treatment effect maintained for ten years (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,880	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,087	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,143	£23,231	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,558	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,509	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,812	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,786	£20,336	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,708	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,328	£22,716
III	Non-Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,596	£26,118
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£15,331	Ext Dominated	£24,846
III	Ischemic	>=150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,284	£28,874
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£14,622	£31,134	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£11,988	£34,614	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,314	£41,379	N/A
IV	Ischemic	>=150ms	OPT	CRTP	CRTD	N/A	Referent	£17,687	£45,925	N/A

Decrease in period of mortality treatment effect

In order to test the impact of a more negative assumption surrounding the duration of all-cause mortality treatment effect, we set the starting point for the tapering off effect to 5 years (base case 7.5 years). The impact of this alternative assumption on the cost-effectiveness of all devices is presented in Table 34 and Table 35.

Overall, truncating the period of treatment efficacy below that observed in long term studies results in an increase in the cost-effectiveness ratios. It is interesting that the model is not only robust to increases in this parameter but also to decreases, since the highest meaningful ICER generated for patients with NYHA I/II heart failure remains below £30,000 per QALY gained. Hence, when the model is executed using overly conservative assumptions, the cost-effectiveness of all interventions is marginal.

Table 34: Deterministic sensitivity analysis – truncation of all-cause mortality treatment effect period (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,136	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,902	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£19,478	£844,105	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,608	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,264	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,349	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,977	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£18,264	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,792	£29,017	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,468	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,797	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,919	£24,221	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£31,354	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£20,968	£24,844
III	Non-Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,540	£25,841
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£28,160	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,871	Ext Dominated	£25,730
III	Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,635	£27,049
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£17,489	£31,552	N/A
IV	Non-Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,472	£35,069	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£24,462	£44,264	N/A
IV	Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£18,205	£38,865	N/A

Table 35: Deterministic sensitivity analysis – truncation of all-cause mortality treatment effect period (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,506	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,469	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£21,205	£25,920	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,439	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,059	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,094	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£21,869	£22,598	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,578	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,872	£25,399
III	Non-Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,098	£29,662
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£15,670	£26,687
III	Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,632	£31,590
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£14,889	£33,237	N/A
IV	Non-Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£12,251	£37,430	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,429	£42,482	N/A
IV	Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,831	£47,651	N/A

Decrease in HRQoL treatment effect period

Despite evidence derived using the long term MLWHF data in our trial database, and the EQ-5D analysis presented in Cleland *et al.*, we have modelled the assumption that the HRQoL treatment effects begin to recede after the average follow up period in the CARE-HF study (circa 2.5 years). The impact of this alternative approach on the cost-effectiveness ratios is presented in Table 36 and Table 37.

HRQoL benefits are greatest in NYHA III/IV patients receiving CRT treatment. In these groups, the truncation of the benefit period has resulted in modest increases in all ICERs. The impact in patients with NYHA I/II heart failure is modest, regardless of treatment option. Hence, the model is robust to changes in this parameter.

Table 36: Deterministic sensitivity analysis – truncation of HRQoL treatment effect period (no LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,068	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,753	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£17,115	£591,782	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,014	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,568	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,361	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,722	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,073	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£19,223	£19,931	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,788	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,967	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,315	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£27,972	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£18,426	£19,141	£28,285
III	Non-Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,985	£24,879
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,992	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£17,734	Ext Dominated	£25,134
III	Ischemic	>150ms	OPT	CRTP	ICD	CRTD	Referent	£12,531	Ext Dominated	£26,218
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£15,638	£31,086	N/A
IV	Non-Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,637	£34,510	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,795	£44,145	N/A
IV	Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,469	£38,478	N/A

Table 37: Deterministic sensitivity analysis – truncation of HRQoL treatment effect period (with LBBB)

			C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,703	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,164	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,120	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,866	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,362	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,858	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,954	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,912	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,161	£24,453
III	Non-Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£7,914	£28,432
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£13,684	Ext Dominated	£25,940
III	Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,937	£30,556
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£12,882	£32,519	N/A
IV	Non-Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£10,602	£36,439	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£20,856	£42,290	N/A
IV	Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,433	£47,256	N/A

APPENDIX 16: Indicative probabilistic sensitivity analyses

As noted in the main text, for reasons of computational complexity we have executed the probabilistic sensitivity analysis for eight patient profiles. Due to the effects of non-decision variables, comparison of these results with those generated for the pooled patient profiles is highly challenging. Nonetheless, these analyses highlight that the deterministic and probabilistic results are broadly aligned (allowing for Monte Carlo error in all calculations).

Male, 65 years old, NYHA II, Ischemic etiology, QRS ≥150ms, LVEF between 20 and 25%, no LBBB

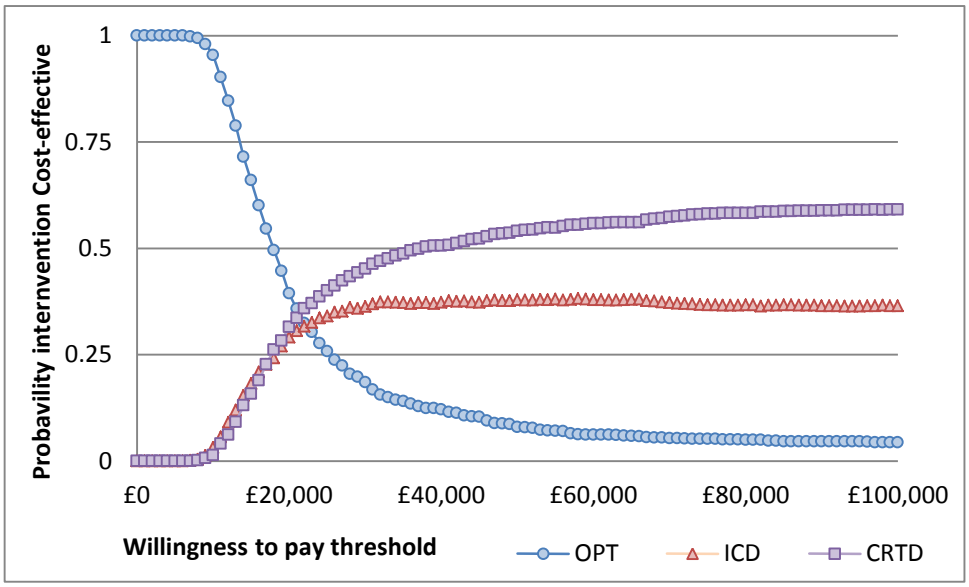
Table 38: Deterministic cost-effectiveness results for sample pt. #1

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£20,613	0.92	Extended Dominated
CRT-D	+£27,336	1.28	£21,330

Table 39: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #1

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£21,627	0.91	Extended Dominated
	(£13,875, £32,277)	(-0.51, 2.22)	
CRT-D	+£28,349	1.20	£23,604
	(£18,503, £42,817)	(-0.51, 2.73)	

Figure 48: Cost-effectiveness acceptability curves for sample pt. #1



Female, 65 years old, NYHA II, Ischemic etiology, QRS ≥150ms, LVEF between 20 and 25%, no LBBB

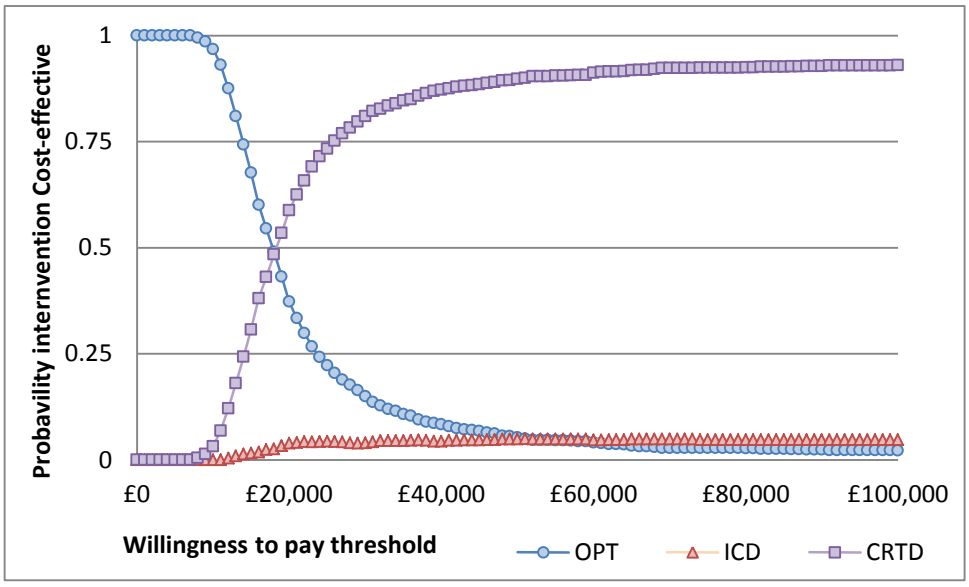
Table 40: Deterministic cost-effectiveness results for sample pt. #2

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£19,736	0.23	Extended Dominated
CRT-D	+£29,170	1.76	£16,565

Table 41: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #2

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£20,640	0.21	Extended Dominated
	(£13,032, £30,556)	(-1.12, 1.43)	
CRT-D	+£30,319	1.66	£18,231
	(£20,305, £44,275)	(0.20, 2.99)	

Figure 49: Cost-effectiveness acceptability curves for sample pt. #2



Male, 65 years old, NYHA II, Ischemic etiology, QRS ≥150ms, LVEF between 20 and 25%, with LBBB

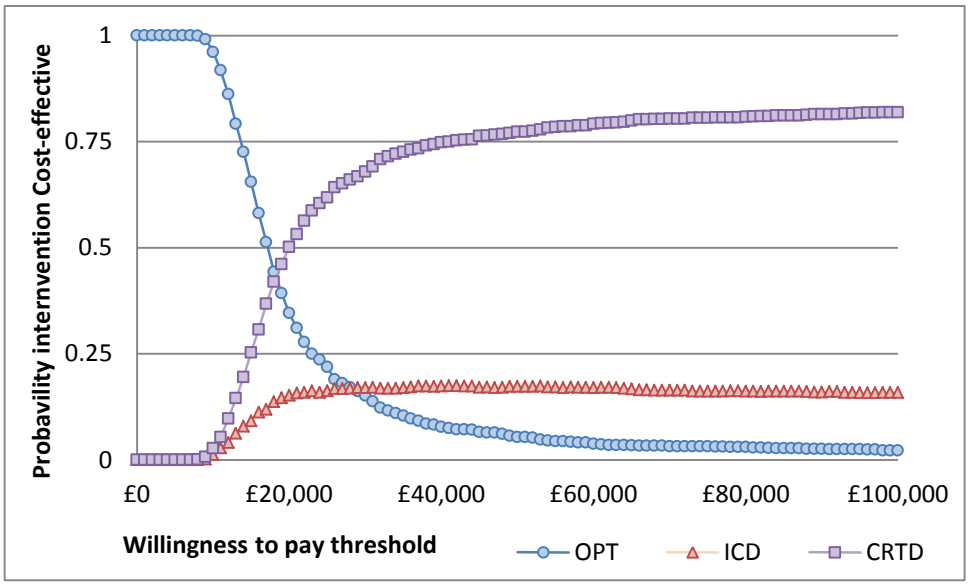
Table 42: Deterministic cost-effectiveness results for sample pt. #3

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	£20,242	0.74	Extended Dominated
CRT-D	£28,116	1.59	£17,645

Table 43: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #3

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£21,171	0.70	Extended Dominated
	(£14,200, £31,123)	(-0.61, 1.98)	
CRT-D	+£29,161	1.52	£19,132
	(£19,331, £43,339)	(0.08, 2.78)	

Figure 50: Cost-effectiveness acceptability curves for sample pt. #3



Female, 65 years old, NYHA II, Ischemic etiology, QRS ≥150ms, LVEF between 20 and 25%, with LBBB

Table 44: Deterministic cost-effectiveness results for sample pt. #4

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	£19,342	0.06	Extended Dominated
CRT-D	£29,849	2.03	£14,718

Table 45: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #4

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£20,248	0.04	Extended Dominated
	(£12,734, £30,594)	(-1.10, 1.22)	
CRT-D	+£31,171	1.93	£16,153
	(£20,783, £45,263)	(0.56, 3.00)	

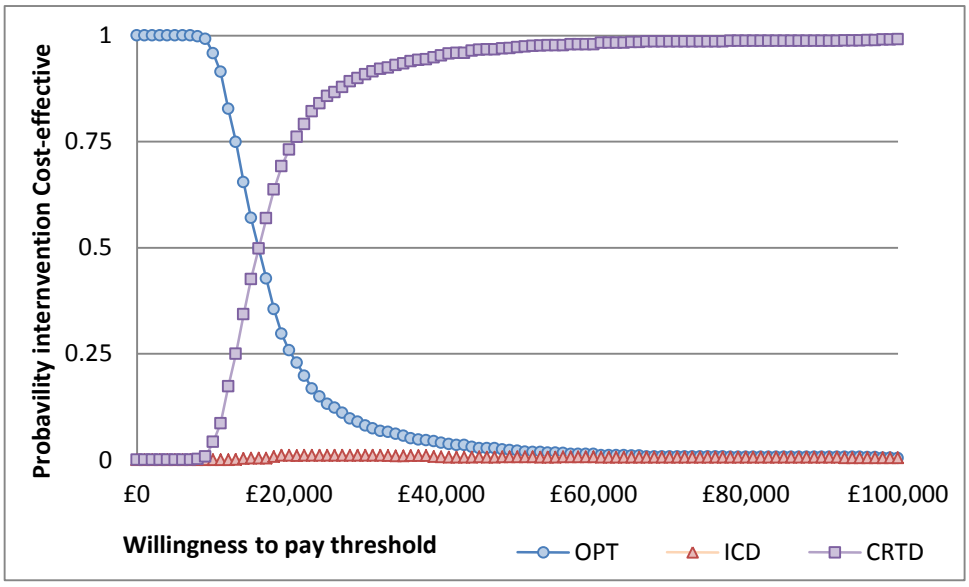



Figure 51: Cost-effectiveness acceptability curves for sample pt. #4