NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

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

This overview is a summary of:

- the assessment report
  - clinical effectiveness, section 4 , pages 12-37
  - cost effectiveness, section 6.21 onwards, pages 52-74
- evidence and views submitted by the manufacturers (joint industry submission)
  - clinical and cost effectiveness, section 6.5-6.20 pages 41-52
- evidence and views submitted by non-manufacturer consultees and their nominated clinical specialists and patient experts, section 5 pages 37-40.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- The joint industry submission and the Assessment Group take different approaches to this appraisal.
  - The manufacturers use individual patient level data from trials, and ask the questions which subgroups are those in which the devices are effective (The manufacturers approach is described in **sections 6.5 to 6.20**.)
  - The Assessment Group uses study level data, and asks the question whether the devices are effective in the populations defined in the scope.

  What are the advantages and disadvantages of each approach?

- The evidence included in the Assessment Group report includes all clinical evidence, that is evidence reviewed in TA95 and TA120, and new evidence.
  What evidence is new and important since the previous NICE appraisal of these devices?

- When deciding whether patients should receive an ICD or CRT, which of the following clinical characteristics should clinicians take into account: NYHA criteria, presence of absence of atrial fibrillation, presence or absence of documented 'dyssynchrony', presence or absence of left bundle branch block, ejection fraction, and /or QT interval on ECG?
- Is an ischemic aetiology important in determining which devices are appropriate for which patients?
- Is it possible to identify patients at high risk for sudden death (who have never had a cardiac arrest), how would this be done, and what level of risk of sudden death is deemed 'high'?
- Trials used in the Assessment Group's study-level meta-analyses differed in population and design. Does the Committee consider that results from the assessment Group's meta-analyses are robust?
- The manufacturers presented network meta-analyses based on patient-level (rather than study-level data). The Assessment Group noted a limited evidence network, partial reporting of the exploratory analyses, lack of long term data and modest power to detect characteristics of patients more or less likely to respond to treatment. Does the Committee consider that results from the manufacturers' network meta-analyses are robust? Does the Committee have enough information about possible interactions between clinical criteria?
- Some of the trials compare the devices to optimal pharmacological therapy which the Assessment Group considers to be not always 'optimal'. Does this bias the results associated with the effectiveness of the devices?

Cost effectiveness

- In the Assessment Group's base-case analyses, patients could crossover and receive a device (or different device) if hospitalised because of heart failure or arrhythmia, using estimates of the risk from trials. Does the Committee consider that this is an appropriate approach to establish the cost effectiveness of the devices? Does the Committee consider that an analysis that explicitly explores a series of the potentially available treatment sequences is required?
- The Assessment Report addendum describes scenario analyses which exclude crossover from the OPT only arm to a device. However, these analyses resulted in slight increases in ICERs for devices compared with OPT. This is because the increased relative benefits were counterbalanced by increase relative costs. What is the Committee' view on these counter-intuitive results?
- The manufacturers' model did not allow crossover. Does the Committee consider that this is an appropriate approach?
- In the Assessment Group model the QALYs accumulated with OPT alone for population 3 were higher than in population 2 although population 3 has a worse prognosis than population 2 (see table 4 and 8, appendix C). Does the Committee consider that these counter-intuitive results point to a lack of robustness of the Assessment Group results?
- The Assessment Group has listed a number of limitations of the manufacturers' cost-effectiveness analyses (see section 6.20). Does the Committee consider that the results from the manufacturers' cost-effectiveness analyses are robust and that the sensitivity analyses provide enough information on what factors drive the model results?
- What factors does the Committee think drive the differences in results based on the Assessment group and manufacturers' models?

1 Background: clinical need and practice.

Arrhythmias

1.1 Arrhythmias occur when the heart contracts irregularly or at a faster or slower pace than normal, caused by an abnormality in the myocardial tissue of the atria or ventricles, or in the electrical conduction system. Arrhythmias that originate from above the ventricles (supraventricular or atrial) are generally not life threatening, but are associated with an increased risk of embolic stroke. Arrhythmias that arise from ventricles (ventricular arrhythmias) can happen suddenly and unexpectedly, and can sometimes be fatal. Ventricular arrhythmias include, among others, ventricular tachycardia and ventricular fibrillation. In ventricular tachycardia the ventricles beat faster than normal (between 120 and 200 beats per minute). In ventricular fibrillation electrical impulses rapidly start firing from multiple sites in the ventricles, resulting in an irregular rhythm and no effective output from the heart to sustain life.

1.2 Ventricular arrhythmias most commonly occur in people with underlying heart disease, including people who are having or had a myocardial infarction (heart attack), people with cardiomyopathy (a disease of the heart muscle), and people who have heart failure. Coronary heart disease, causing myocardial infarction leading to the ventricular tachycardia or ventricular fibrillation, is the most common clinical finding associated with sudden cardiac deaths, accounting for 80% of such deaths. Cardiomyopathies account for a further 10% to 15% of sudden cardiac deaths and there is likely to be significant overlap between this group and those with coronary heart disease. The remaining 5-10% of sudden cardiac deaths are associated with either structurally abnormal congenital cardiac conditions or structurally normal hearts with electrical abnormalities. People at higher risk of

sudden cardiac deaths include those who have previously survived a life-threatening arrhythmia, hemodynamic abnormalities including heart failure and acute coronary syndromes such as myocardial infarction and angina pectoris. However, in over 30% of sudden cardiac deaths, heart disease had either not been previously diagnosed or people were known to have cardiac disease but were considered to be at low risk for sudden cardiac death.

1.3 The Assessment Group estimate that around 75-80% of the estimated 70,000 sudden cardiac deaths in England and Wales in 2010 could be attributed to ventricular arrhythmias. The average survival of adults with an out of hospital cardiac arrest has been reported as low as 7%. With appropriate treatment and secondary preventive strategies, recent studies have reported 5 year survival of 69 to 100%. Preventing sudden cardiac death in someone who has never had a cardiac arrest or ventricular arrhythmia (primary prevention) is challenging in clinical practice because it requires identifying people with a sufficient level of risk, and an optimal strategy for risk stratification is currently lacking.

1.4 Treatment of ventricular arrhythmias acutely can consist of shocking a patient with an external defibrillator and then offering anti-arrhythmic drug therapy and other drug treatments specific to the underlying heart disease. Prophylactic anti-arrhythmic drug therapy aims to suppress the development of arrhythmias, but does not terminate an arrhythmia once it is initiated. People with arrhythmias at risk of sudden cardiac death may be given an implantable cardioverter defibrillator (ICD) device to detect and treat such arrhythmia. NICE technology appraisal guidance 95 recommends ICDs for both secondary prevention (that is, prevention of a further life-threatening event in survivors of a sudden cardiac episode or patients with recurrent unstable

rhythms) and primary prevention (that is, prevention of a first-life threatening arrhythmic event). For secondary prevention an ICD is recommended in people who have survived a cardiac arrest because of ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation) and in people with spontaneous sustained ventricular tachycardia causing syncope or significant hemodynamic compromise or who have LVEF of less than 35% but clinically are no worse than New York Heart Association (NYHA) class III of heart failure. For primary prevention it is recommended in people with a familial cardiac condition with a high risk of sudden death (for example long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia), or in people who have undergone surgical repair of congenital heart disease. It is also recommended as primary prevention in people with previous (more than 4 weeks) myocardial infarction (MI) who also have either LVEF of less than 35% but clinically are no worse than NYHA class III of heart failure and non-sustained VT on Holter monitoring plus inducible VT on electrophysiological testing or LVEF of less than 30% but clinically are no worse than NYHA class III of heart failure and have a QRS duration of equal to or more than 120 milliseconds.

Heart Failure

1.5 Heart Failure is a condition caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently as a pump to support circulation. It is characterised by breathlessness, fatigue and fluid retention. Clinically it is classified using the NYHA functional class, ranging from Class I (no limitation of physical activity) to Class IV (symptomatic at rest and discomfort from any physical activity). Heart failure is also classified based on which heart function or which side of the heart is most affected:

some patients have heart failure due to left ventricular systolic dysfunction (LVSD) which is associated with a reduced left ventricular ejection fraction (left heart failure or biventricular failure); while others have only right heart failure with a preserved ejection fraction The scope for this appraisal focuses on left and biventricular heart failure.

1.6 Heart failure is a chronic condition predominantly affecting people over the age of 50 years. The incidence of heart failure in the UK is 140 per 100,000 men and 120 per 100,000 women. Approximately 900,000 people in England and Wales have heart failure, of which at least half have LVSD. The incidence and prevalence of heart failure increases with age and the average age at first diagnosis is 76 years. People with heart failure are at risk from sudden cardiac death, which is the most common cause of death in people with mild to moderate heart failure. Progressive failure of the heart's ability to pump is usually the cause of death in case of severe heart failure.

1.7 Treatment of heart failure aims to improve life expectancy and quality of life. NICE clinical guideline 108, "Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care" recommends treating heart failure due to LVSD with angiotensin converting enzyme (ACE) inhibitors and beta-blockers. If a person then remains symptomatic, the guideline recommends adding one of the following as second-line treatment: an aldosterone antagonist licensed for heart failure (e.g. spironolactone) (especially NYHA class III–IV) or has had a recent MI] or an angiotensin II receptor antagonist (ARB) licensed for heart failure [especially if NYHA class II–III)] or hydralazine in combination with nitrate [especially if the patient is of African or Caribbean origin and has NYHA class III–IV)]. Other drugs recommended for heart failure include diuretics, calcium channel

blockers, amiodarone, anticoagulants, aspirin and inotropic agents (such as dobutamine, milrinone or enoximone. However, as the condition becomes more severe, cardiac function and symptoms may no longer be controlled by pharmacological treatment and require invasive procedures. Cardiac function and heart failure symptoms may be improved by the implantation of a cardiac rhythm device which can sense and stimulate the atria, right and left ventricles independently. The devices are known as cardiac resynchronisation pacemaker (CRT-P) or cardiac resynchronisation defibrillator (CRT-D). The decision to implant CRT is also guided by left ventricular ejection fraction. NICE technology appraisal 120 'Cardiac resynchronisation therapy for the treatment of heart failure' recommends CRT-P as a treatment option for people with heart failure who fulfil all the following criteria: are currently experiencing or have recently experienced NYHA class III–IV symptoms; are in sinus rhythm - either with a QRS duration of 150 ms or longer estimated by standard ECG or with a QRS duration of 120–149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography; have a LVEF of ≤35%; are receiving OPT. 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 NICE technology appraisal guidance 95.

2 The technologies

Implantable cardioverter defibrillators (ICDs)

2.1 ICDs are small, battery powered devices that are implanted under the skin, typically just below the collarbone, with leads (tiny wires) into the heart. The devices operate by sensing and analysing the electrical activity of the heart thereby monitoring for arrhythmia and delivering electrical pulses or shocks to restore normal sinus rhythm. Based on average selling prices aggregated across all

manufacturers of ICDs sold in the UK to the NHS, the cost for ICDs was estimated at £9,692 for the whole system.

Cardiac resynchronisation therapy pacing device (CRT-P)

2.2 Cardiac resynchronisation therapy (CRT-P), also known as biventricular pacing, involves implanting a pulse generator in the upper chest to resynchronise the contraction of the ventricles, thereby improving pumping efficiency and increasing blood flow to the body. Based on average selling prices aggregated across all manufacturers sold in the UK to the NHS, the cost for CRT-P is at £3,411for the whole system.

Cardiac resynchronisation defibrillators (CRT-D)

2.3 CRT-Ds combine CRT-P and ICD devices. A CRT-D defibrillates the heart internally in an acute arrhythmic event and improves ventricular efficiency and blood flow. Based on average selling prices aggregated across all manufacturers sold in the UK to the NHS, the cost for CRT-D is at £12,293 for the whole system.

2.4 Adverse events are mostly related to implantation-related complications and include coronary vein dissection, coronary vein perforation, lead dislodgement, infection and death. For details of adverse events related in the trials please see section 4.10, 4.30 and 4.43 and 4.55.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of implantable cardioverter defibrillators in the treatment of arrhythmias and biventricular pacing (cardiac resynchronisation) to restore synchronous cardiac contraction in patients with advanced heart failure.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment People with both conditions described above	This group includes and expands on the population considered in TA 95. For the present assessment this population is not restricted by NYHA classification and there is no specified cut-off for LVEF. The second group includes and expands on the population considered in the previous TA 120. As in the TA120, this population is not restricted by NYHA classification but unlike it there is no specified cut-off for LVEF. The third group, people with both conditions, were not considered in the previous technology appraisals.

People with cardiomyopathy are not excluded from consideration in this assessment.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Intervention	Implantable cardioverter defibrillators (ICDs) in addition to optimal pharmacological treatment Cardiac resynchronisation therapy (CRT-P or CRT-D) in addition to optimal pharmacological treatment Cardiac resynchronisation therapy with a defibrillator device (CRT-D) in addition to optimal pharmacological treatment	No additional comments or specifications.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Comparators	For People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment: • standard care (optimal pharmacological treatment without ICD) For people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment: • CRT-P and CRT-D will be compared with each other • standard care (optimal pharmacological treatment without CRT) For people with both conditions: • ICD • CRT-P • standard care (optimal pharmacological treatment alone)	The Assessment Group noted that a standard definition of optimal pharmacological treatment (OPT) was difficult because the concepts of OPT have changed over time and also depend on the patient population being treated, for example patients with previous ventricular fibrillation, post MI, or heart failure receive different pharmacological treatment. The Assessment Group included all studies that compared ICDs or CRTs with the different types of medical therapy and reported the details of the pharmacological therapy. The clinical-effectiveness section of this report therefore describes this as 'medical therapy', specifying where the Assessment Group noted this to be 'optimal' by current standards.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Outcomes	• mortality (may include progressive heart failure mortality, non heart failure mortality, all cause mortality and sudden cardiac death) • adverse effects of treatment • health related quality of life • symptoms and complications related to tachyarrhythmias and/or heart failure • heart failure hospitalisations • change in NYHA class • change in left ventricular ejection fraction	No additional comments or specifications.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	No additional comments or specifications.

4 Clinical-effectiveness evidence

4.1 The Assessment Group conducted a systematic review of the literature and identified 26 relevant randomised controlled trials (RCTs): 13 trials comparing ICD with medical therapy in people at increased risk of sudden cardiac death as a result of ventricular arrhythmias (population 1); 4 trials comparing CRT-P (and CRT-D in one trial) with medical therapy in people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony, (population 2) and 9 trials comparing CRT-D with ICD in people with both of these conditions (population 3).

People at risk of sudden cardiac death as a result of ventricular arrhythmias (population 1)

4.2 The Assessment Group highlighted that all 13 RCTs identified were unblinded and therefore at high risk of bias, particularly in the context of quality of life outcomes. The trials used different criteria to identify groups at 'high risk' of sudden cardiac death from ventricular arrhythmia as categorised below:.

People with ventricular arrhythmia/cardiac arrest (secondary prevention)

4.3 The AVID (n=1016), CASH (n=288), CIDS (n=659) and DEBUT (n=66; pilot – 20 and main study – 46) trials evaluated ICD in combination with medical therapy compared with medical therapy

alone, as in people who had previous ventricular arrhythmia or had been resuscitated from cardiac arrest (secondary prevention). The DEBUT trial included people of Thai origin who had survived sudden unexplained death syndrome with otherwise normal hearts. The average length of follow-up varied from 18 months to 57 months across the trials. All participants in the CASH trial, 90% in the CIDS trial and 60% in the AVID trial had congestive heart failure, with more than 80% (CASH) and 50% (AVID, CID) classed as NYHA I and II. All participants in the DEBUT trial had NYHA class 1 congestive heart failure, and were also younger with a mean age of 40-48 years compared with a mean age of 56 to 65 years in the other trials. LVEF varied from 30% to 70% across the trials.

4.4 All four trials assessed all-cause mortality as the primary outcome measure. The Assessment Group noted that only the CASH trial was adequately powered to detect a difference in all-cause mortality and reported a risk ratio of 0.82 (95% CI 0.60 to 1.11) for ICDs compared with medical therapy. The AVID and the main DEBUT trials reported all-cause mortality risk ratios of 0.66 (95% CI 0.51 to 0.85) and 0.09 (95% CI to 1.57) respectively for ICDs compared with medical therapy. The CIDS trial reported a risk ratio of 0.85 (95% CI 0.67 to 1.10) for ICD compared with medical therapy. The Assessment Group conducted a meta-analysis of the results from the AVID, CASH, CIDS and 20 people in the pilot DEBUT trial and results indicated a benefit for ICDs compared with medical therapy, with a risk ratio of 0.75 (95% CI, 0.61 to 0.93; p=0.010).

4.5 The AVID and CIDS trial reported total cardiac death risk ratios of 0.67 (95% CI 0.50 to 0.90) and 0.81 (95% CI 0.61 to 1.08) respectively for ICDs compared with medical therapy. The Assessment Group's meta-analysis of the two studies indicated

that a benefit on cardiac death of ICDs compared with medical therapy with a risk ratio of 0.74 (95% CI, 0.61 to 0.91; p=0.004). The AVID and CIDS trials found no differences between the ICDs and medical therapy for non-arrhythmic cardiac deaths and a meta-analysis conducted by the Assessment Group supported these findings reporting a risk ratio of 0.97 (95% CI 0.72 to 1.31; p=0.83). Results from the Assessment Group's meta-analysis found no effect of ICDs on non-cardiac deaths 0.79 (95% CI 0.45 to 1.37; p=0.40).

4.6 The rates of sudden cardiac death were lower with ICDs compared with medical therapy in all 4 trials and a meta-analysis conducted by the Assessment Group indicated a benefit for ICDs compared with medical therapy with a risk ratio of 0.49 (95% CI, 0.34 to 0.69; p<0.0001). The AVID trial reported a benefit on overall survival at 3 years (difference 11%, p<0.02), survival free of cardiac death at 2 years (difference 4%, p=0.004) and survival to arrhythmic death at 2 years (difference 5%, p=0.0002) for ICDs compared with medical therapy. The CASH trial also reported a benefit on survival free of sudden death at 57 months with a HR of 0.42 (p=0.005) and trends towards benefits on overall survival (HR 0.77, p=0.081) and survival free of cardiac arrest (HR 0.48, p=0.072) for ICDs compared with medical therapy.

4.7 The AVID trial reported the proportion of patients re-hospitalised during follow up finding higher rates for the ICD group compared with the medical therapy group at 3 years (83% compared to 75.5%; p=0.04).

4.8 The AVID and CIDS trials assessed quality of life through separate sub-studies using a range of generic and condition-specific measures of quality of life. The AVID trial reported that there were no statistically significant differences in SF-36 scores between groups at 12 month follow-up. The Assessment Group noted that,

at baseline, the ICD group reported worse score on the mental component of the SF-36 compared with the medical therapy group, but there was no difference between groups at 12 month follow-up. Adverse symptoms and ICDs shocks were reported to have a negative impact on quality of life scores for ICD across the different measures. A sub-study of the CIDS trial reported that quality of life improved significantly for the ICD group, between baseline and 12 month follow up, on 3 domains of the Mental Health Inventory (MHI) and 5 out of 7 domains on the Nottingham Health Profile (NHP), while there was no improvement in the medical therapy group and the domains of energy level and physical mobility deteriorated. The quality of life of those experiencing more than 5 ICD shocks did not differ significantly on the MHI and the NHP from the medical therapy group. Those experiencing no shocks and between 1 and 4 shocks reported significant improvements on the MHI and NHP with ICDs compared with medical therapy.

4.9 While all 4 trials reported adverse events, the events reported differed, therefore limiting comparison across trials. Direct comparisons of adverse events between the ICDs and medical therapy were also limited: the DEBUT trial reported that that 30% of people with ICDs and 14% of people with medical therapy experienced adverse events; the AVID trial compared deaths within 30 days of initiation of therapy or by hospital discharge if 30 days after initiation of therapy, and reported no statistically significant differences between the ICDs and medical therapy. In contrast, the CASH trial reported statistically significantly higher mortality rates during the perioperative period for ICDs (5.1%) compared with medical therapy (1.1%).

4.10 The AVID trial presented four pre-specified subgroup analyses for all-cause mortality based on age, LVEF, cause of arrhythmia and

qualifying arrhythmia. The results for all-cause mortality did not differ from the overall population for any of the subgroups.

4.11 The most frequently reported adverse events with ICDs included defibrillation discharges caused by superventricular tachycardia or sinus tachycardia (19%, DEBUT); T-wave oversensing (8%, DEBUT); product discomfort (7.6%, CIDS); ICD permanently or temporarily explanted due to infection, heart transplantation or patient preference (5%, DEBUT); device dysfunction (5%, CASH); pocket erosion requiring removal of ICD (3%, DEBUT); dislodgement or migration of system leads (3%, CASH); ICD dislodgement/fracture (2.4%, CIDS); bleeding requiring reoperation or transfusion (1.2%, AVID);and, unsuccessful first attempt at ICD implantation without thoracotomy (1.0%, AVID). Other adverse events included: haematoma or seroma (6%, CASH); serious haematoma (2.6%, AVID); pleural effusion (3%, CASH); infection (2.0%[AVID] to 4.6% [CIDS]);and, pneumothorax (1.6%, AVID).

People with a recent myocardial infarction (primary prevention)

4.12 The DINAMIT (n=674) and IRIS (n=898) trials compared ICD in combination with medical therapy with medical therapy alone in people with a myocardial infarction within the previous 6 to 40 days, or within 5 to 31 days respectively. The Assessment Group highlighted that medical therapy in both trials, which included antiplatelet agents, beta-blockers and lipid lowering agents including statins, met current standards of optimal management. The Assessment Group stated that the block randomisation in the unblinded DINAMIT trial could have lead to a prediction of allocation and bias. In addition, in the IRIS trial the ICD group had a higher proportion of people with left-bundle-branch block (10.1% vs. 6.4%, p=0.05) and diabetes mellitus (37.2% vs. 30.2%, p=0.03) than the medical therapy group. Average length of follow-up was 30

and 37 months respectively. Approximately 60% of people in both trials were in NYHA class II, Most of the remaining were NYHA class III in the DINAMIT trial and NYHA class I in the IRIS trial Mean LVEF was 28% in the DINAMIT trial and 35% in the IRIS trial.

4.13 Result from both trials were supported by results from a meta-analysis of the two trials conducted by the Assessment Group which reported no benefit in all-cause mortality (RR 1.04, 95% CI, 0.86 to 1.25; p=0.69), total cardiac deaths (RR 0.97, 95% CI, 0.79 to 1.20; p=0.8) or non-cardiac deaths (RR 1.39, 95% CI, 0.86 to 2.27; p=0.18) with ICDs compared with medical therapy. However, people receiving ICDs had a lower risk of sudden cardiac death (RR 0.45, 95% CI, 0.31 to 0.64; p<0.0001), but a higher risk of non-arrhythmic cardiac death (RR 1.77, 95% CI, 1.30 to 2.40; p=0.0002) compared with people receiving medical therapy. The IRIS trial found no statistically significant difference between groups for cumulative mortality. Quality of life was not reported in either study. In the IRIS trial, 15.7% patients in the ICD group experienced clinically significant complications requiring hospitalisation, surgical correction, or intravenous drug administration and 1.7% patients died within 30 days of implantation surgery. In 3.4% of patients, ICD was explanted or permanently deactivated because of complications. No participant in DINAMIT died because of a complication with the device but 8.1% of patients experienced device-related complications.

4.14 The IRIS trial included 13 pre-specified subgroup analyses for all cause-mortality. Statistically significant differences were found in favour of medical therapy for people who received thrombolytic therapy for early reperfusion of ST-elevation MI and statistically significant differences were found in favour of ICD in combination with medical therapy for people with left main artery disease.

People with remote myocardial infarction (primary prevention)

4.15 The MADIT I (n=196 and MADIT II (n=1232 trials compared ICD in combination with medical therapy with medical therapy alone, in people who had an episode of myocardial infarction at least three weeks or one month prior to study entry respectively. Average length of follow-up was 27 months for MADIT 1 and 20 months for MADIT II. Approximately 70% of people in both trials had NYHA class II or III symptoms and the remaining had NYHA class I symptoms. Mean LVEF was approximately 26% in MADIT 1 and 23% in MADIT II.

4.16 Both the MADIT I and MADIT II trials reported a reduction in all-cause mortality with ICDs compared with medical therapy reporting hazard ratios of 0.46 (95% CI 0.26 to 0.82, p=0.009) and 0.69 (95% CI, 0.51 to 0.93; p=0.016) respectively and these results were supported by a meta-analysis conducted by the Assessment Group. Post-trial follow-up of MADIT II found continued benefit with ICDs at 8 years with a HR of 0.66 (95% CI 0.56 to 0.78, p=0.001). The meta-analysis also supported the finding from the trials with regard to some secondary outcomes for ICDs compared with medical therapy, reporting a RR of 0.59 (95% CI, 0.42 to 0.83; p=0.003) for total cardiac deaths, a RR of 0.36 (95% CI, 0.23 to 0.55; p<0.00001) for sudden cardiac death. No differences between groups were found in the trials for non-arrhythmic cardiac deaths or for non-cardiac deaths, supported by results from the meta-analysis which reported RR of 0.95 (95% CI, 0.41 to 2.18; p=0.9) and 1.06 (0.58 to 1.95; p=0.84) respectively. The MADIT II trial reported a similar hospitalisation rate per 1000 months follow-up (ICDs 11.3, OPT 9.4, p=0.09). It also reported that the proportion of hospitalisations due to heart failure was higher with ICDs (ICDs 19.9%, OPT 14.9 %,) but the statistical significance was not stated.

4.17 The MADIT II trial assessed quality of life through the Health Utility Index (HUI3), reporting that scores were lower (worse) in people in the ICD group (0.637) compared with medical therapy (0.646) at baseline and that differences were not statistically significant between groups at 3 years follow-up (ICD 0.019, medical therapy 0.013, p value not reported). The MADIT II trial also reported 12 pre-specified subgroup analyses for all-cause mortality. The Assessment Group stated that the hazard ratios were similar in all subgroups, with no statistically significant interactions.

People with non-ischemic or idiopathic dilated cardiomyopathy (primary prevention)

4.18 The AMIOVIRT (n=103), CAT (n-=104) and DEFINITE (n=458) trials compared ICD in combination with medical therapy alone with medical therapy in people with non-ischemic or idiopathic dilated cardiomyopathy, with follow-up ranging from 24 months to 29 months. The Assessment Group stated that the medical therapy in all the AMIOVIRT and DEFINITE trials met current standards for optimal management (see table 15 on page 75 of the Assessment Report for further details). The medical therapy in the CAT trial was not considered optimal by current standards due to low beta-blocker use. The CAT trial enrolled people with recently diagnosed with heart failure. However, despite participants not having suffered ventricular arrhythmias, the Assessment Group highlighted that a low LVEF of <30% indicates risk of ventricular arrhythmias and sudden cardiac death, so the trial was considered eligible for inclusion. Participants in CAT had a median duration of symptoms of 3 months, compared to around 3 years in AMIOVIRT and DEFINITE. They were also younger with a mean age 52 years compared with 58 and 59 years in DEFINITE and AMIOVIRT. The majority of participants in all 3 trials were in NYHA class II or III,

with none in NYHA class IV. Mean LVEF ranged from 21% to 25% across the trials.

4.19 None of the trials reported a statistically significant difference in all cause mortality with ICD in combination with medical therapy compared with medical therapy, with a risk ratio of 0.87 (95% CI 0.32 to 2.42) in the AMIOVIRT trial, a risk ratio of 2.16 (95% CI 0.41 to 11.28) in the CAT trial and a risk ratio of 0.70 (95% CI 0.45 to 1.09) in the DEFINITE trial. These results were supported by a meta-analysis by the Assessment Group which reported an all-cause mortality risk ratio of 0.77 (95% CI, 0.52 to 1.15). The meta-analysis also found no statistically significant differences between groups for non-arrhythmic cardiac death (RR 1.13, 95% CI, 0.42 to 3.03). In addition, a meta-analysis of the AMIOVIRT and CAT trials found no statistically significant differences between groups for total cardiac deaths (RR 2.03, 95% CI, 0.17 to 23.62), or non-cardiac death (RR 0.65, 95% CI, 0.13 to 3.29;). The CAT trial reported substantially worse outcomes in the ICD group for non-arrhythmic cardiac death as well as total cardiac death, but these results were not statistically significant. A meta-analysis of the AMIOVIRT and DEFINITE trials found a statistically significant reduction for sudden cardiac death with ICDs, with a risk ratio of 0.26 (95% CI, 0.09 to 0.77; p=0.02).

4.20 The AMIOVIRT and CAT trials reported no statistically significant difference in survival. The AMIOVIRT trial assessed changes in quality of life using the Quality of Well Being Schedule (QWBS) and the State Trait Anxiety Inventory (STAI) and reported no statistically significant difference between the groups at 1 year follow up. Although the DEFINITE trial assessed quality of life using the SF-12 mental (MCS) and physical (PCS) component scores and MLHFQ, and stated that no statistically significant differences were

found between groups, the Assessment Group stated that no data were reported.

4.21 The DEFINITE trial reported six pre-specified subgroup analyses for all-cause mortality. The differences were statistically significant for the subgroups of men, in people with NYHA class III heart failure and in people with LVEF ≥20% for ICD compared with medical therapy.

People scheduled for CABG surgery (primary prevention)

4.22 The CABG Patch trial (n=900) compared ICD combined with medical therapy compared with medical therapy alone in people who were scheduled for coronary artery bypass graft surgery and were at risk of sudden cardiac death. The Assessment Group noted that the medical therapy in this trial would have been considered optimal when the trial was conducted, but that it was not optimal by current standards and the excess use of anti-arrythmytic drugs in the ICD arm may have offset some of the benefits from ICD. The mean follow-up was 32 months and mean LVEF was 27%. The majority of participants were in NYHA class II or III.

4.23 The results showed risk ratios of 1.08 for all-cause mortality (95% CI 0.85 to 1.38), of 0.98 for total cardiac deaths (95% CI 0.74 to 1.30), of 1.26 for non-arrhythmic cardiac death (95% CI 0.87 to 1.82), of 1.50 for non-cardiac death (95% CI 0.82 to 2.73) and of 0.55 for sudden cardiac death (95% CI 0.30 to 1.01) for the ICD group compared with medical therapy.

4.24 The CABG Patch trial assessed health related quality of life using measures of perception of health, ability to function and psychological well-being at 6 months follow-up. Health related quality of life scores were lower with ICDs compared with medical therapy for all measures, and the results were statistically

significant for measures of perception of health transition, emotional role function, mental health, satisfaction with appearance and satisfaction with scar.

4.25 The CABG Patch trial evaluated 10 pre-specified subgroups (age, gender, heart failure, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs). It reported that the hazard ratios for all-cause mortality with ICDs compared with medical therapy were similar among the subgroups. However, the Assessment Group noted that the actual data were not reported.

People with mild to moderate heart failure (secondary prevention)

4.26 The SCD-HeFT three-arm trial (n=2521)) compared ICD in combination with medical therapy, medical therapy and placebo in combination with medical therapy alone, in a broad population of patients with mild-to-moderate heart failure due to ischaemic or non-ischaemic causes. The Assessment Group highlighted that the medical therapy in this trial could be considered optimal by current standards. Mean follow-up was 46 months and mean LVEF was 25%. Over 70% of participants were in NYHA class II, and the remaining were in NYHA class III.

4.27 The primary outcome of all-cause mortality was reduced with ICDs compared with the combined placebo and medical therapy group with a hazard ratio of 0.77 (97.5% CI, 0.62 to 0.96; p=0.007). Reductions in total cardiac death were also found with ICDs compared with the combined placebo and medical therapy groups with a hazard ratio of 0.76 (95% CI, 0.60 to 0.95; p=0.018) and for sudden cardiac death with a risk ratio of 0.44 (95% CI 0.31 to 0.61; p<0.00001). For non-arrhythmic cardiac death or deaths from non-

cardiac causes, there were no differences between ICDs and the control arm with risk ratios of 1.14 (95% CI 0.88 to 1.48) and 0.92 (95% CI 0.66 to 1.27) respectively.

4.28 The SCD-HeFT trial reported health related quality of life scores at baseline, 3, 12 and 30 months follow-up using the Duke Activity Status Index (DASI), Mental Health Inventory 5 (MHI-5), Minnesota Living With Heart Failure (MLHFQ) and the global health status. The only statistically significant differences between ICDs and placebo were in median MHI scores and global health status at 3 and 12 months, but these differences were not maintained at 30 months; and the MLHFQ score at 3 months but this benefit was not maintained at 12 months. A significant decrease in perceptions of quality of life was found using the SF-36 among people who had received an ICD shock within the previous month compared with those who had not received a shock.

4.29 The SCD-HeFT trial reported pre-specified subgroup analyses for all-cause mortality and cause of death according to cause of congestive heart failure and NYHA class (class II or III). There was no interaction of ICD therapy (p=0.68) with the cause of congestive heart failure (ischaemic or non-ischaemic) for all-cause mortality or other specified modes of death. However, there was an interaction between ICD therapy and NYHA class (p<0.001). Compared with placebo, ICDs reduced the risk of all-cause mortality, cardiac mortality and sudden cardiac death in people with NYHA class II but not in those with NYHA class III.). The interaction between ICD therapy and NYHA class was not statistically significant for heart failure (p=0.29) or non-cardiac (p=0.11) deaths.

4.30 The 9RCTS evaluating ICDs for primary prevention reported adverse event rates between 5% (SCD-Heft) and 61% (CABG Patch) in people with an ICD, depending on the definition of adverse event and length of follow-up. Adverse event rates for the

comparator treatment were between12% to 55% in the three RCTs reporting it. Lead, electrode or defibrillator generator related problems affected 1.8% (MADIT II) to 14% (CAT) of people in the five trials that reported it.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony (population 2)

4.31 The Assessment Group identified 4 multicentre RCTs comparing CRT-P with medical therapy in people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony. The CARE-HF (n=813) and COMPANION (n=1520) trials were unblinded, and therefore at high risk of bias. The MIRACLE (n=453) and MUSTIC (n=58) trials were blinded as investigators implanted all participants with a CRT-P device, but inactivated the device in the control group. The MUSTIC trial used a randomised crossover design, with 3 months follow-up for each of the two cross-over periods and the Assessment Group stated that the crossover design was appropriate. The details of randomisation methods and allocation concealment methods were not reported in the COMPANION, MIRACLE and MUSTIC trials. The Assessment Group stated that the medical therapy included in all 4 trials was optimal by current standards (page 149 of the Assessment Report). The COMPANION trial also compared CRT-P with CRT-D and CRT-D with medical therapy; however, the Assessment Group stated that the trial was not powered for the comparison of CRT-P with CRT-D. All trials included people with NYHA class III or IV heart failure, with the majority of participants in NYHA class III (82% [CARE-HF] to 100% [MUSTIC]) and with LVEF less than 35%. Average LVEF was about 22% in MIRACLE and COMPANION, and 25% in CARE-HF. Though the QRS duration criteria differed across trials, (that is for CARE-HF and COMPANION ≥120 ms, MIRACLE≥130 ms and MUSTIC ≥150ms)

the mean QRS interval was approximately 160 ms across all 4 trials.

4.32 Studies differed in the timing of implantation, baseline evaluation and randomisation. In particular, the Assessment Group noted that only those participants with a successful implantation underwent randomisation in the MUSTIC and MIRACLE trials, limiting the generalisability of these studies. Although an intention to treat analysis was performed in the trials, the proportion of patients in the medical therapy group who switched to a CRT was high ranging from 4% in MIRACLE to 42% in COMPANION.. The primary outcomes in the COMPANION and CARE-HF trials were composite endpoints of all-cause mortality and all-cause hospitalisation in COMPANION, and all-cause mortality and unplanned hospitalisation for a major cardiovascular event in CARE-HF. The primary outcome of MIRACLE and MUSTIC was distance walked in 6 minutes. Changes in NYHA class and quality of life were also primary outcomes in MIRACLE. The results reported from the trials are summarised below.

CRT-P compared with medical therapy

4.33 The CARE-HF trial reported a difference in all-cause mortality after a mean follow-up of 37.4 months, with a risk ratio of 0.60 (95% CI 0.47 to 0.77, p<0.0001) for CRT-P compared with medical therapy. This difference persisted during long-term follow-up of 343 of 813 people originally enrolled despite implantation of CRT devices in more than 95% of those originally assigned to the medical therapy group (HR 0.77, 95% CI 0.63 to 0.93, p=0.007). Differences in all cause mortality observed in the other 3 trials were not statistically significant. A meta-analysis of the results of all 4 trials conducted by the Assessment Group found that CRT-P statistically significantly reduced the risk of all-cause mortality compared with

medical therapy with a risk ratio of 0.75 (95% CI 0.58 to 0.96, p=0.02).

4.34 The COMPANION and MUSTIC trials measured total cardiac death and reported no statistically significant difference between the CRT-P and medical therapy groups. The COMPANION trial also found no statistically significant differences between groups for non-cardiac deaths. All trials reported sudden cardiac death, although the Assessment Group noted uncertainties with the MIRACLE trial data because the numbers in each arm were not reported and the total sample size in the FDA report (n=536) differed from the number randomised in the main publication (n=453). In the CARE-HF trial, fewer patients randomized to CRT-P experienced sudden cardiac deaths compared with medical therapy with a risk ratio of 0.59 (95% CI 0.39 to 0.89). The COMPANION and MUSTIC trials did not report any statistically significant difference between groups. The Assessment Group conducted a meta-analysis which demonstrated no difference in risk of sudden cardiac death between the CRT-P and medical therapy groups with a risk ratio of 0.97 (95% CI 0.44 to 2.14).

4.35 In the CARE-HF trial, fewer patients randomized to CRT-P died from heart failure compared with medical therapy with a risk ratio of 0.59 (95% CI 0.40 to 0.86). The COMPANION trial, however, found no statistically significant differences between groups reporting a risk ratio of 0.78 (95% CI 0.52 to 1.17). A meta-analysis by the Assessment Group found that CRT-P relative to medical therapy delayed the time to death with a risk ratio of 0.67 (95% CI 0.51 to 0.88, p=0.004).

4.36 All 4 trials measured hospitalisations attributed to heart failure and all except MUSTIC reported lower rates of hospitalisation from heart failure with CRT-P compared with medical therapy. The Assessment Group's meta-analysis showed a risk ratio for

hospitalisation due to heart failure of 0.61 (95% CI, 0.44 to 0.83; p=0.002). Data on the number of events of hospitalisation attributed to heart failure and/or number of days of hospitalisations due to heart failure were reported in three trials (CARE-HF, COMPANION and MIRACLE) but no statistical analyses were reported. The Assessment Report calculated the rate of hospitalisation due to heart failure for each trial and combined these in a meta-analysis. This demonstrated a significant reduction in the rate of heart failure hospitalisations with CRT-P compared to medical therapy (RR 0.58, 95% CI 0.35 to 0.96, p=0.03). Three trials (CARE-HF, MIRACLE and MUSTIC) reported a benefit with CRT-P for 'worsening of heart failure', the criteria for which differed across the trials. When the trials were combined in a meta-analysis, the risk of worsening heart failure was lower with CRT-P (RR 0.71, 95% CI 0.63 to 0.80, p<0.00001) than with medical therapy. These trials (CARE-HF, COMPANION and MIRACLE) also reported a greater proportion of participants with improvement in NYHA class with CRT-P than with medical therapy. The Assessment Group conducted a meta analysis which showed an increase in the proportion of people with an improvement in one or more NYHA class with CRT-P compared with medical therapy (RR 1.68; 95% CI, 1.52 to 1.86; p<0.00001).

4.37 The CARE-HF trial reported that the risk of arrhythmias was higher with CRT-P compared with medical therapy with a risk ratio of 1.54 (95% CI 1.07 to 2.23, p=0.02). The CARE-HF, COMPANION and MIRACLE trials reported a statistically significant greater proportion of patients with an improvement in NYHA class with CRT-P compared with medical therapy. The Assessment Group's meta-analysis of these trials for an improvement in one or more NYHA class with CRT-P compared with medical therapy, estimated a risk ratio of 1.68 (95% CI 1.52 to 1.86, p<0.00001).The MIRACLE trial measured change in LVEF and reported an improvement with

CRT-P at 6 months, with an increase of 4.6%, compared with a decline of 0.2% with medical therapy.

4.38 The COMPANION, MIRACLE and MUSTIC trials reported that CRT-P improved exercise capacity more than did medical therapy, as measured by the distance walked in 6 minutes. A meta-analysis of these trials showed a change from baseline to final reported walking distance, with a mean difference of 38.14 m, 95% CI 21.74 to 54.54, ($p<0.00001$).

4.39 All 4 trials assessed change in the health related quality of life using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ). CARE-HF also reported EQ-5D, mean QALYs and mean life-years. All trials found that CRT-P improved MLWHFQ score compared with medical therapy and a meta-analysis by the Assessment Group indicated a mean difference of -10.33 (95% CI, -13.31 to -7.36, $p=0.00001$). CARE-HF also reported improvements in EQ-5D, with a mean increase of 0.13 in the EQ-5D scores for CRT-P compared with medical therapy (95% CI 0.08 to 0.18, $p=0.0001$). In addition, the mean number of QALYs was higher with CRT-P at 18 months (CRT-P 0.95 vs. medical therapy 0.82, $p<0.0001$) and also at the end of the study (1.45 vs. 1.22, <0.0001).

4.40 Only CARE-HF reported pre-specified subgroup analyses. Of 17 subgroups, the investigators reported a significant interaction only between CRT-P and the presence of absence of ischaemic heart disease: people without ischemic heart disease experienced a greater improvement in LVEF than people with ischaemic heart disease.

CRT-D compared with medical therapy

4.41 Data from the COMPANION trial were available for a comparison of CRT-D with medical therapy. Results from this trial reported

reductions or delays with CRT-D compared with medical therapy for the outcomes of all-cause mortality (HR 0.64, 95% CI 0.48 to 0.86, p=0.003), total cardiac deaths (RR 0.68, 95% CI 0.50 to 0.93, p=0.02), sudden cardiac deaths (HR 0.44, 95% CI 0.23 to 0.86, p=0.02) and heart failure hospitalisations (RR 0.77, 95% CI 0.63 to 0.93, p=0.008). In addition, the proportion of people with an improvement of one or more NYHA class (57% vs. 38%, p<0.001), improvements in exercise capacity (change in 6 MWT 46 m vs. 1 m, p<0.001), and health related quality of life scores at 6 months measured by MLWHFQ score (-26 vs. -12, p<0.001) were statistically significantly greater with CRT-D compared with medical therapy. There were no differences between the CRT-D group and the medical therapy group for the outcomes of heart failure deaths (HR 0.73, 95% CI 0.47 to 1.11, p=0.143) and non-cardiac deaths (CRT-D 2.3% vs OPT 3.6%, p=0.717).

CRT-P compared with CRT-D

4.42 Data from the COMPANION trial were available for a comparison of CRT-P with CRT-D. However, the Assessment Group highlighted that the trial was not powered for to compare CRT-P with CRT-D and therefore all results for this comparison should be interpreted with caution. The results indicated that total cardiac deaths and sudden cardiac deaths were higher with CRT-P compared with CRT-D with risk ratios of 1.38 (95% CI 1.06 to 1.81, p=0.02) and 2.72 (95% CI 1.58 to 4.68, p=0.0003) respectively. The results were for all-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, p=0.12), heart failure deaths (RR 0.98, 95% CI 0.68 to 1.42, p=0.93), heart failure hospitalisations (28% vs. 29%). Changes in NYHA class, exercise capacity and health related quality of life scores were not statistically significantly different between CRT-P and CRT-D.

4.43 The Assessment Group stated that the reporting of adverse events was limited in all 4 trials. The MIRACLE and MUSTIC excluded

patients with unsuccessful implantation (7.5% and 7.8% of enrolled patients) while the rate of unsuccessful implantation was 6% in CARE-HF and 12.6% in COMPANION. Device-related deaths reported in the trials varied between 0.2% (MIRACLE and CARE-HF) and 0.8% (COMPANION) for those with CRT-P and 0.5% for those with CRT-D (COMPANION). In COMPANION moderate or severe adverse events related to implantation procedure was 10% with CRT-P and 8% with CRT-D, with 13% and 9% of CRT-P and CRT-D implantations unsuccessful. Reported complications included lead displacements, infections and coronary-sinus dissections.

People with heart failure as a result of LVSD and cardiac dyssynchrony who are also at risk of sudden cardiac death as a result of ventricular arrhythmias (population 3)

4.44 The Assessment Group identified 9 trials comparing CRT-D with ICDs in people at risk of sudden cardiac death due to ventricular arrhythmia and with heart failure as a result of LVSD and cardiac dyssynchrony. In 6 trials (CONTAK-CD [n=490], MIRACLE ICD [n=369], MIRACLE ICD II [n=186], Pinter [n=72], RethinQ [n=172] and Rhythm ICD [n=179]), all patients were implanted with a CRT-D, that is, a device that could provide both CRT and ICD therapy, but the CRT function was switched off in the comparator group, therefore providing active ICD therapy only. In 3 trials (MADIT-CRT [n=1820], RAFT [n=1798] and Piccirillo [n=31]), the comparator group received an ICD only device. Participants also received medical therapy (except in the Piccirillo trial) and the Assessment Group stated that, in general, the medical therapy was optimal by current standards (see page 195 of the Assessment Report). No trials comparing CRT-D with medical therapy or with CRT-P were identified for this population.

4.45 The Piccirillo trial was a single-centre study conducted in Italy. All other trials were multicentre trials with largely North American centres. Only the MADIT-CRT trial included a UK centre. The ReTHINQ and RHYTHM ICD trials were described as double-blind but the Assessment Group stated that details were not reported. The Assessment Group also stated that apart from the MADIT-CRT trial, no details were available on the methods of randomisation method or blinding. The MADIT-CRT trial was considered to be at high risk of bias because diagnosis of heart failure and decisions on therapy or hospital admission were made by physicians who were aware of study group assignments. The RAFT trial was considered to have a high risk of selective reporting bias because outcomes stated in the protocol were not reported in the publication. The study design of CONTAK-CD was modified from a randomised crossover design with crossover to occur after 3 months of randomised therapy (Phase I), to a parallel RCT design with 6 months of follow-up (Phase II) and data from both phases are reported.

4.46 The trials differed in their eligibility criteria for severity of heart failure. Most patients in MADIT-CRT, MIRACLE ICD II and RAFT were in NYHA class II while in CONTAK-CD, MIRACLE ICD, RethinQ and RHYTHM ICD majority of patients were in NYHA class III. NYHA class was not reported by Pinter, although the eligibility criteria specified mild to moderate heart failure. The majority of patients in Piccirillo were in NYHA class I. The proportion of patients with ischemic heart disease varied between the trials, from approximately 52% in the RethinQ trial to 100% in the Piccirillo trial. Average length of follow-up ranged between 6 to 40 months across the trials. Prolonged QRS duration on ECG (more than 120 ms to more than 150 ms in different trials) was used to define cardiac dyssynchrony in all the trials except in the RethinQ in which people with a narrow QRS interval (less than130

ms) were included on the basis of mechanical dyssynchrony apparent on echocardiograph. Mean left ventricle ejection fraction ranged from 21% (CONTAK-CD) to 26% (RethinQ). Crossover between groups was reported by 6 the trials and crossover from the ICD to the CRT-D treatment arm ranged from 2.8% (Pinter) to 12.4% (MADIT-CRT) of patients, the most common reason for crossover was heart failure events. Crossover from CRT-D to ICD ranged from 0% (RethinQ) to 7.5% (MADIT-CRT) of patients, most commonly because of difficulties with the implanted device. The MADIT-CRT, Piccirillo and RAFT trials randomised participants before or at the time of implantation. The CONTAK-CD trial implanted the device first because of the immediate need for ICD therapy, then programmed the randomised therapy after a minimum 30 day period with no CRT, during which time investigators were permitted to optimise pharmacologic therapy. The other studies randomised only those participants in whom the implanted were successful and the time of randomisation varied between from 7 to 28 days after implantation.

4.47 The Assessment Group stated that only 4 trials were adequately powered to show a difference in their primary outcomes which were death or non-fatal heart-failure events (MIRACLE ICD), left ventricular end-systolic volume change from baseline (Pinter), composite outcome of death from any cause or heart failure leading to hospitalisation (RAFT) and proportion of patients with an improved peak oxygen consumption during cardiopulmonary exercise testing and survival from CRT-D system related complications (ReTHINQ) . However, the Assessment Group highlighted that the MIRACLE ICD trial was not powered to detect a morbidity or mortality difference. Of the remaining trials, the CONTAK-CD and MADIT-CRT trials were not considered to be adequately powered and the MIRACLE ICD II and RHYTHM ICD trials did not report sample size calculations. The Piccirillo trial was

a small study of 31 participants which did not report sample size calculations, and because mortality and NYHA were not primary outcomes the Assessment Group assumed that it was not powered for these outcomes.

4.48 All trials reported data on all-cause mortality, but not as a primary outcome, and only the MADIT-CRT and RAFT trials compared the results statistically. The MADIT-CRT trial found no statistically significant difference in all-cause mortality with a risk ratio of 0.94 (95% CI 0.67 to 1.32) while the RAFT trial found a statistically significant reduction in mortality with CRT-D compared with ICDs with a risk ratio of 0.80 (95% CI 0.67 to 0.94). The Assessment Group's analysis of reported data from the remaining trials suggested no statistically significant difference in all-cause mortality between groups in any of the trials. In the Piccirillo trial no deaths were observed in both groups. The Assessment Group also conducted a meta-analysis pooling data from the trials which found that compared to ICDs, CRT-D reduced the risk of all-cause mortality significantly with a risk ratio of 0.84 (95% CI 0.73 to 0.96, p=0.01). The Assessment Group commented that the results were strongly influenced by the RAFT trial and when this study was removed from the analysis the differences were no longer statistically significant.

4.49 All but the MADIT-CRT and Piccirillo trials reported data on total cardiac deaths, although only the RAFT trial compared results between groups statistically. It found that CRT-D was associated with a statistically significant reduction in cardiac deaths compared with ICDs with risk ratio of 0.76 (95% CI 0.60 to 0.96). When these trials were combined in a meta-analysis by the Assessment Group, the overall risk ratio was 0.82 (95% CI 0.67 to 1.00, p=0.05) in favour of CRT-D compared with ICDs. The results were no longer significant if the RAFT study was excluded from the meta-analysis.

The CONTAK-CD, MIRACLE ICD II, Piccirillo and ReTHINQ trials reported data on deaths from heart failure and sudden cardiac death. In addition, the MICRACLE ICD and RHYTHYM ICD trials reported data on sudden cardiac death. Deaths due to heart failure or sudden cardiac death were not statistically significantly different between the CRT-D and ICD groups in any of the trials reporting it as well as in the meta-analyses conducted by the Assessment Group .The pooled risk ratio for death due to heart failure, for CRT-D compared with ICD was 0.64 (95% CI 0.18 to 2.22, p=0.48) while for sudden cardiac death it was 1.45 (95% CI 0.43 to 4.92, p=0.55). No statistically significant differences between groups for 6-month cumulative survival was reported by the MIRACLE ICD or RethinQ trials with rates of 92.4% and 94.2% for the CRT-D group respectively and rates of 92.2% and 98.8%, for the ICD group respectively. The RAFT study indicated that the probability of event-free survival at 5 years was 57.6% with CRT-D and 48.7% with ICD but statistical significance was not reported.

4.50 The RAFT, CONTAK-CD and Piccilrillo trials reported hospitalisations related to heart failure. The RAFT trial found a statistically significant reduction in heart failure hospitalisations with CRT-D compared with ICD with a risk ratio of 0.75 (95% CI 0.63 to 0.89; p=0.0009). The CONTAK-CD and Piccirillo trials found no significant difference between groups but combining all 3 trials in a meta-analysis demonstrated that CRT-D statistically significantly reduced the risk of hospitalisation by 25% compared with ICD with a risk ratio of 0.75 (95% CI 0.64 to 0.88, p=0.0005). The CONTAK-CD, MICRACLE ICD, MIRACLE ICD II and Pinter trials reported the number of participants experiencing at least one episode of ventricular tachycardia or ventricular fibrillation. The Assessment Group stated that the proportions were similar between groups across the trials and a meta-analysis demonstrated no statistically significant difference in the number of people experiencing at least

one arrhythmia with a risk ratio of 0.90 (95% CI 0.71 to 1.14, p=0.38).

4.51 All except the Pinter and RAFT trials reported change in NYHA class. The MIRACLE ICD, MIRACLE ICD II and RHYTHM ICD trials reported a statistically significant improvement in mean or median NYHA class among people with CRT-D compared with people with ICD. Combining these studies in a random effects meta-analysis resulted in a statistically significant mean difference of -0.19 (95% CI -0.34 to -0.05, p=0.008). The CONTAK-CD, ReTHINQ and Piccirilli trials reported the proportion of people who improved by one or more NYHA class; the RethinQ and Piccirillo trials found a statistically significant improvement with CRT-D compared with ICDs but the CONTAK-CD trial found no statistically significant difference between groups in the number of people with improvement in NYHA class. The meta-analysis of these studies showed no statistically significant difference between two groups with a risk ratio of 1.81 (95% CI 0.91 to 3.60).

4.52 Three trials (CONTAK-CD, MADIT-CRT, MIRACLE ICD II) reported a statistically significant improvement from baseline in mean LVEF among people with CRT-D compared with ICD, whereas three trials (MIRACLE ICD, Pinter, RethinQ) reported no statistically significant difference between the groups in change from baseline. The Piccirillo and RHYTHM ICD trials reported data but did not provide a statistical analysis of change in LVEF. The Assessment Group's own assessment of the data from the Piccirillo trial indicated a statistically significant improvement with CRT-D compared with ICD, but the results from RHYTHM trial did not indicate any statistically significant differences. The Assessment Group's meta-analysis indicated a statistically significant improvement in LVEF with CRT-D compared with ICD with a mean difference in mean LVEF of 2.15 (95% CI 0.45 to 3.86, p=0.01).

4.53 All except the RAFT and Piccirillo trials reported change in exercise capacity measured by either distance walked in 6 minutes, measuring exercise duration, measuring peak VO2 (peak oxygen uptake), and by proportion of participants with an increase of at least 1.0 ml/kg body weight/minute in peak oxygen consumption. The Assessment Group's meta-analysis indicated that there was a greater improvement in exercise capacity with CRT-D than with ICD, as demonstrated by change from baseline in peak VO2, with data pooled from 5 trials indicating a mean difference of 0.75 ml/kg body weight/minute between groups (95% CI 0.23 to 1.27, p=0.005) and as demonstrated by distance walked in 6 minutes, with data pooled from 6 trials indicated a mean difference of 14.5 meters between groups (95% CI 2.9 to 26.1, p=0.01).

4.54 All except the RAFT and Piccirillo trials reported changes in quality of life at 6 months using the MLWHF questionnaire. Meta-analysis of these trials indicated an statistically significant improvement in quality of life with CRT-D compared with ICD with a mean difference of -6.9 in MLWHFQ scores between groups (95% CI -10.4 to -3.4, p=0.0001). The Pinter trial also reported statistically significant improvements between groups for the General Health component of the SF-36 when comparing baseline to 6 month changes.

4.55 The Assessment Group stated that reporting of adverse events was inconsistent between the trials. The RAFT trial compared adverse events between groups statistically and found that device or implantation related complications within 30 days of implantation were significantly higher in the CRT-D group than the ICD group (13.3% compared with 6.8%, p<0.001), as was device-related hospitalisation (20% compared with 12.2%, p<0.001), lead-dislodgement requiring intervention (6.9% compared with 2.2%) and coronary sinus dissection (1.2% compared with 0). After the

first 30 days, MADIT-CRT reported 4.5 serious device-related adverse events per 100 device-months with CRT-D compared with 5.2 events with ICD.

4.56 Three trials (MADIT-CRT, RAFT and RethinQ) reported pre-specified subgroup analyses. The MADIT-CRT and RAFT trials reported that CRT-D was associated with a greater benefit in people with QRS duration 150 ms or more than in those with QRS duration of less than 150 ms with p-values of interaction of 0.001 in the MADIT-CRT trial and of 0.002 in the RAFT trial. The ReTHINQ trial found significant improvements in the proportion of people with an improvement in peak oxygen uptake with CRT-D in those with QRS ≥ 120ms but not for those with QRS <120ms. CRT-D was also associated with greater benefit in women than in men (MADIT-CRT; p-value for interaction 0.01) and in people with left bundle branch block (LBBB) than in those with nonspecific intraventricular conduction delay (RAFT; p-value for interaction 0.046). The RethinQ trial found a statistically significant improvement with CRT-D in distance walked in 6 minutes for those with non-ischemic cardiomyopathy (55.0 m vs. 2.5 m, p= 0.01) but not for those with ischemic cardiomyopathy (4.2 m vs. 5.8 m, p=0.57). Other subgroups analyses did not show any statistically significant effects (see page 236 of the Assessment Report for further details).

5 Comments from other consultees

5.1 Consultees submitted a comprehensive review of the clinical effectiveness of ICD and CRT as well as a perspective of the place of the technology in current practice. It noted that many healthcare professionals are involved in the identification, treatment and follow-up of patients with indications for ICD and CRT therapy. These include primary and secondary care physicians to identify patients and cardiologists specialising in electrophysiology, device therapy or heart failure who are primarily responsible for

determining whether device therapy is indicated, subsequently implanting the devices and providing specialist clinical follow-up along with nurses who play a major part in the follow-up of patients. Consultees emphasised that long-term coordination of these healthcare professionals is essential for optimal care.

5.2 Consultees also commented that multiple trials have shown that anti-arrhythmic drugs may alleviate symptoms but do not improve prognosis in patients with life-threatening arrhythmias and the only effective treatment for these patients is an ICD. It was noted that ICDs have become safer to implant, that they have become more reliable in avoiding unnecessary therapy and also have significantly improved battery life. Indications for ICD implantation have evolved from purely secondary prevention after a resuscitated cardiac arrest, to include primary prevention in those at high risk of sudden cardiac death. In addition, it was noted that a simple assessment based on LVEF and underlying cardiac disease can predict those who benefit from ICD implantation. Similarly, it was noted that CRT has revolutionised the treatment of severe heart failure in those with cardiac dyssynchrony and a simple assessment based on LVEF and the duration of the QRS complex on the standard ECG can predict those who are likely to benefit.

5.3 Consultees stated that in the UK, implantation rates remain well-below rates in Western Europe or North America and analysis of the National Devices Database and other audits shows that access to device therapy is not uniform across the UK, suggesting that failure to identify patients suitable for device therapy was a reason for this disparity. Consultees suggested that simplification of indications and investigations in line with trial evidence and international guidelines would reduce this inequity of access.

5.4 Consultees noted that the main advantage of ICD implantation is that it reduces the risk of sudden death while CRT implantation

reduces the burden of heart failure symptoms and mortality. Disadvantages include the discomfort of implantation procedures, associated complications, regular device follow-up and social effects including restriction of driving. Consultees also mentioned that the clinical trials have demonstrated that the benefits of device therapy remain significant and sustained and highlighted that adverse events can be minimised by appropriate patient selection, highly competent implantation and follow-up services using remote technologies.

5.5 In the review of clinical effectiveness presented by a consultee, it was highlighted that superiority of ICD over medical therapy for secondary prevention has been well established and it is considered unethical to perform further clinical trials in this population. For primary prevention, it found that left ventricular function is a significant predictor of risk while non-sustained ventricular tachycardia, ventricular tachycardia induced by programmed electrical stimulation and QRS duration have limited sensitivity or specificity to predict those who will and will not benefit from ICD implantation. It also commented that since measurement of LVEF is not very accurate in clinical practice, a single threshold of equal or less than 35% should be used. For CRT it noted that patients with severe left ventricular impairment (LVEF ≤35%) and evidence of dyssynchrony on ECG (QRS ≥120ms) and heart failure symptoms despite optimal pharmacological therapy, benefit from CRT with improved symptoms, reduced hospitalisation and reduced all-cause mortality. Other measures of mechanical dyssynchrony have not shown sufficient sensitivity and specificity to be clinically useful in the identification of patients who will benefit from CRT.

5.6 Comments were received from one patient organization emphasising the importance of primary prevention, ensuring

screening for those who are at risk of arrhythmias that lead to sudden cardiac arrest and may require an ICD or CRT device.

6 Cost-effectiveness evidence

Assessment Group literature review

6.1 The Assessment Group conducted a systematic literature review to identify published health economic evaluation studies relevant to this appraisal. It identified that the cost effectiveness of ICD and CRT had been evaluated in 34 and 16 studies respectively, and that 2 of these studies included the evaluation of both ICD and CRT. These studies were published between 1990 and 2012, and most of them were conducted in North America. Most of these studies employed state transition models to estimate long term outcomes extrapolated from short-term outcomes in the trials and time horizons varied from 3 years to a lifetime. Most of the studies were based on a single trial, with MADIT II and SCD-HeFT being the most common trials for ICD evaluation and CARE-HF and COMPANION being the most common trials for CRT evaluation.

6.2 For ICD therapy, the Assessment Group stated that it considered only 5 studies to be of high methodological quality. Of these, it considered only one study (Buxton et al., 2006) relevant from a UK perspective. This study used a Markov model with a 20 year time horizon to evaluate the cost-effectiveness of ICD compared with medical therapy in people patients at risk of sudden cardiac death with previous CA or VT, using data from the CIDS, CASH and AVID trials and data from observational studies. It reported a mean ICER of £76,139 per QALY gained, and this decreased to £48,372 per QALY gained in people with low LVEF when the time horizon was extended to a lifetime. However, the Assessment Group highlighted that this study used data from before 2002 and therefore the results may not be generalisable to current practice.

6.3 For CRT, almost all studies reported that CRT was cost effective compared with medical therapy, with only two studies uncertain as to whether CRT was cost effective compared with medical therapy. The Assessment group considered 6 studies to be of high methodological quality, two of which were the studies reporting uncertainty about cost-effectiveness of CRT compared with medical therapy. Of these, one study (Fox et al.) was considered relevant from a UK perspective. This study reported a Markov model to compare CRT-P and CRT-D with medical therapy in people with heart failure in the UK over their lifetime. People were in NYHA class III and IV with LVEF ≤35% and QRS direction >120 ms. It estimated an ICER of £16,735 per QALY gained for CRT-P compared with medical therapy, and an ICER of £40,160 per QALY gained for CRT-D compared with CRT-P. CRT-D was more likely to be cost-effective compared with CRT-P, in subgroups of people who are younger or those with high risk of sudden cardiac death who would qualify for CRT.

6.4 Bertoldi et al. 2011 evaluated the cost-effectiveness of CRT-D compared with ICD. The Assessment Group noted that this was conducted in Brazil using a Markov model and reported that in people with heart failure (NYHA class II-IV and LVEF less than 35%) CRT-D compared with ICDs was associated with an ICER of $36,940 per QALY gained.

Manufacturer's submission

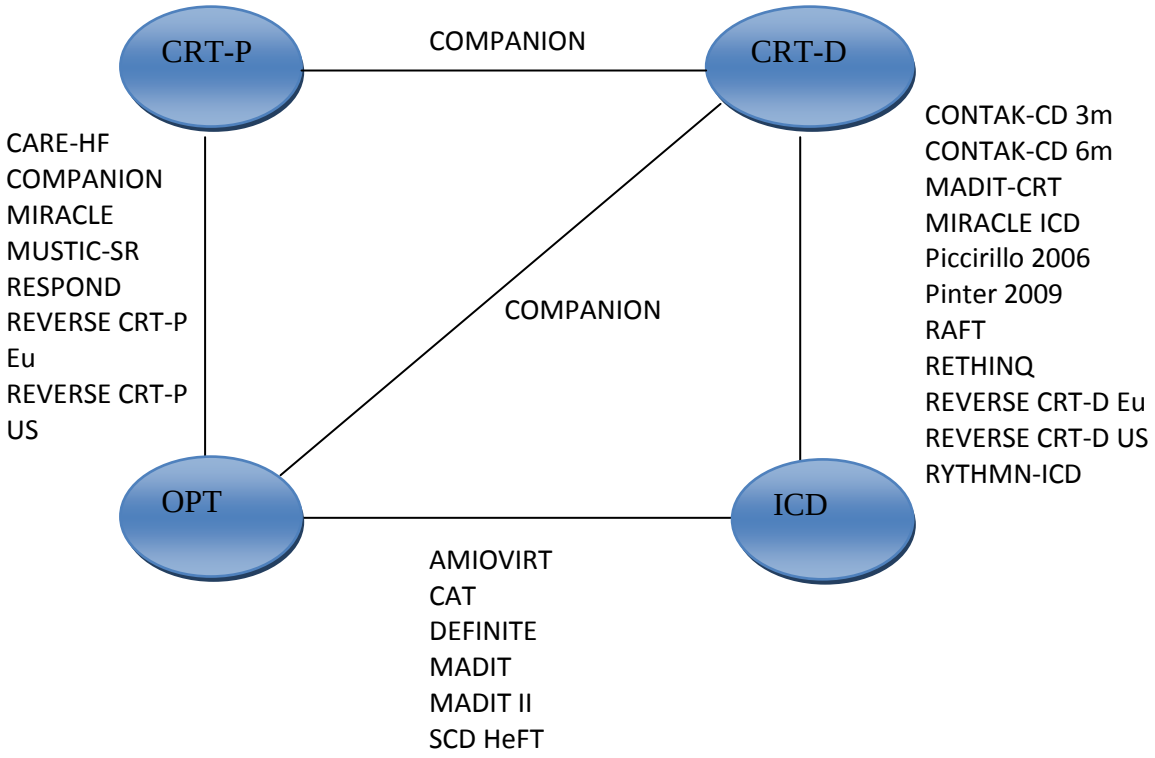
6.5 The Association of British Healthcare Industries (ABHI) submitted a joint submission on behalf of the five major device manufacturers relevant to this submission (Biotronik UK, Boston Scientific, Medtronic UK, Sorin Group and St Jude Medical). The submission included a systematic review of published studies of clinical effectiveness of OPT, ICD, CRT-P and CRT-D for the treatment of cardiac arrhythmias and heart failure, and an economic evaluation

with which to determine the patients, based on clinical parameters, in whom the different devices (ICD, CRT-P, or CRT-D) would be most cost- effective. The focus of this economic evaluation is different from the scope as it does not address the 3 populations specified in the scope. The manufacturers highlighted that they used individual patient characteristics to define the populations as the population in most of the trials did not match the groups defined in the scope. In addition, the manufacturers' submission focused solely on the use of ICD for primary prevention, commenting that people who meet the criteria laid in TA95 for secondary prevention (in particular having survived a cardiac arrest) have a strong clinical indication for an ICD, that there was a the reduction in implant costs, as well as the absence of new studies in this patient group. The Assessment Group stated that while the interventions compared in the submission were consistent with the NICE scope, not all of them were included as comparators for all patient subgroups in the submission because no patients were identified for these combinations: for example, ICD was excluded for NYHA class IV, CRT-P was excluded for NYHA class I/II and QRS <120ms and CRT-D was excluded for QRS <120ms. The Assessment Group stated that these exclusions appeared to be reasonable based on clinical opinion.

6.6 The manufacturers conducted a systematic review of the literature and identified 22 relevant trials. The manufacturers stated that this indicated that there is a large body of RCT evidence available confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with heart failure. The manufacturers also stated that no new evidence was identified relating to the use of ICD for secondary prevention of ventricular arrhythmia.

6.7 The manufacturers' presented an individual patient data network meta-analysis using meta-regression to assess the effectiveness of

ICDs, CRT-P and CRT-D in the different sub-groups of people who have heart failure. The results for the outcomes relevant to economic analysis, that is, all-cause mortality, all cause hospitalisation and health related quality of life were synthesised and incorporated in the modelling. The Assessment Group stated that with limited published evidence on the effectiveness of devices in different patient sub-groups with heart failure, the availability of individual patient data makes a network meta-analysis meta-regression possible and justified.



Network of randomised controlled trials

6.8 Individual patient data from 13 of the 22 trials identified in the systematic review was available to inform the individual patient

data network meta-analysis. These 13 trials included the COMPANION, CONTAK-CD, MADIT, MADIT II, MADIT-CRT, CARE-HF, MIRACLE, MIRACLE-ICD, RAFT, REVERSE, SCD-HeFT, DEFINITE and RethinQ trials. These trials included 95% of the total number of patients across all 22 trials. The Assessment Group commented that 7 trials identified in the Assessment Report (DINAMIT, IRIS, CABG Patch, AVID, CASH, CIDS, DEBUT) were not included in this analysis. However, the Assessment Group noted that issues concerning differences in the 13 trials relating to the effects of length of follow-up, trial cross-over, missing data and data handling were discussed in the submission. Length of follow-up was limited to that specified in the trials' protocols to limit the effects of trial cross-over at longest follow-up. Missing data for the covariables appeared limited, with data imputed through multiple imputations where necessary. In addition, the covariables used to capture baseline risk and treatment effect modifiers in the NMA were outlined for the different outcomes assessed, with the rationale for their inclusion and for any data manipulation discussed.

6.9 The data for all-cause mortality were aggregated from 13 trials, all-cause hospitalisation from 11 trials and health related quality of life from 3 trials. However, the Assessment Group noted that the submission outlined reasons for excluding specific studies from the overall evidence network, the approach taken to allocating trials to different comparisons and the basis for handling data. Different types of regression were used for analysing the three outcomes, and these are presented on pages 247 and 248 of the Assessment Report. The Assessment Group stated that although it was not possible to provide a detailed critique of each stage in the three analyses given the partial reporting of the exploratory and confirmatory analyses undertaken or to replicate the network meta-analysis, the steps taken and the results appeared to be

reasonable, noting that several concerns described in section 6.8 has been addressed in the submission.

6.10 The network meta-analysis found CRT-D to have the strongest effect on all-cause mortality with a hazard ratio of [redacted] compared with medical therapy. The hazard ratio for all-cause mortality was [redacted] for CRT-P compared with medical therapy and [redacted] for ICD compared with medical therapy. The hazard ratio for all-cause mortality for CRT-D compared with CRT-P was [redacted] and for CRT-D compared with ICD it was [redacted]. For all cause-hospitalisation, the network meta-analysis indicated that 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 was more pronounced, with CRT associated with a [redacted] reduction in admission rates (although the data used to inform this result are sparse). Baseline estimates of health related quality of life using the EQ-5D from the network-meta-analysis showed that patients in NYHA I and II had similar values to the population norms, while patients in NYHA III and IV had values that were progressively lower. Some of the treatment estimates showed counter-intuitive results, for example results for CRT-D for NYHA III and IV class showed a decrease in health related quality of life, in contrast to those for CRT-P, possibly reflecting the limited individual patient data available. As a consequence, adjustments were made that assumed that CRT-P and CRT–D had the same effect on EQ-5D values and that ICDs had an effect on the quality of life of NYHA I and II only. The Assessment Group noted that for all-cause mortality, network meta-analyses were produced to compare outcomes with those using aggregate data from all trials in the network, finding no significant

differences. Similar comparisons were not produced for the other outcomes.

6.11 The manufacturers' submission included a survival-based model to estimate the relative cost-effectiveness of OPT, ICD, CRT-P and CRT-D, compared with each other. The UK NHS and PSS perspective was adopted and the model had monthly cycles and a lifetime time horizon. Costs and health benefits were discounted at 3.5%.The model has two health states: alive and dead. The manufacturers stated that death is the main clinical event for the patient population considered in this appraisal and by modelling death directly via a series of covariate based regression equations (for baseline risk and treatment effect), the long term data available could be used to explore the impact of patient-level heterogeneity. The manufacturers stated that this approach would also allow for a coherent regression-based approach to modelling health related quality of life and all-cause hospitalisation that was aligned with the mortality analysis, and that the alternative approach to capture the effect on health related quality of life using time-dependent progression through NYHA classes was technically difficult and less accurate. The Assessment Group stated that the fundamental features of the condition and the impact of the interventions seem to be captured in the manufacturers' model structure and while no assessment of internal validity of the model was included in the submission, it appeared to be intuitive.

6.12 Individual patient data from 12,638 patients were used to inform the manufacturers' economic model. Modeled patients were adults with heart failure with LVEF ≤35%, and/or at risk of sudden cardiac death. This heterogeneous group of patients was split into 48 subgroups according to their NYHA class, QRS duration, left bundle branch block (LBBB) status and aetiology of heart disease, and cost-effectiveness results are reported for each subgroup. In

order to model baseline mortality risk, a parametric survival curve (Weibull) was fitted to a pooled data set of all patients randomised to medical therapy in the included trials. The base-line probability of all-cause hospitalisation was estimated in a similar manner using individual patient data from 11 clinical trials. The relative effectiveness of the devices was estimated from individual patient data network meta-analysis as discussed in section 6.9.UK device longevity estimates were derived from NHS data from the Central Cardiac Audit Database on all implants with verified life status from 2000 to 2011 (around 40,000 implants). Device specific median survival estimates were obtained by fitting Weibull curves to this data. Median time to device failure in the model was 7.1 years for ICD, 10.4 years for CRT-P and 5.8 years for CRT-D.

6.13 The manufacturers' model does not include short-term device related adverse events as the costing approach used to derive total implant costs covered additional costs such as short term adverse events. Infection following device was included in the model for all procedures subsequent to the initial implant. The proportion of patients experiencing infection was estimated to be 0.8% and applied to all devices in the first cycle following battery replacement.

6.14 The resource use included device-related costs, medication, and resources related to disease progression. Individual patient data from the trials was used to estimate the mean number of all cause hospitalisation events per month and the mean number of days of hospitalisation per month. The hospital costs were derived from the NHS Schedule of Reference Costs and combined with the average mean length of hospital stay. The cost of hospitalisation because of heart failure was £2,295 and the non-heart failure hospitalisation cost was £2,448. Device costs were sourced from the average selling prices across the manufacturers for ICD, CRT-P and CRT-D

devices and leads sold in the UK to the NHS. The implantation costs were taken from the Healthcare Resource Group tariff values. . Device costs, including implantation costs, were estimated to be £15,248, £8,281 and £17,849 for ICD, CRT-P and CRT-D respectively. The Assessment Group stated that, overall, the derivation of costs and assumptions presented in the submission appeared to be appropriate and consistent with previous approaches.

6.15 The manufacturers' assumed that medical therapy which was considered optimal by current standards, that is, OPT was received by all patients for heart failure treatment, regardless of whether they received a device in addition. It was also assumed that the drug cost allocated in any given month to each patient was based on their baseline NYHA class. The proportion of patients using a range of medications, by NYHA class, was derived from a combination of the clinical studies identified in the systematic review and expert opinion. The recommended daily dose for each commonly used drug was sourced from the British National Formulary (BNF). The total cost of OPT treatment per 1 month cycle was £14.28 for NYHA class I and between £22.13 and £22.30 for NYHA class II-IV.

6.16 For modelling utility, general UK population utilities based on a study of 3,395 individuals resident in the UK were used at baseline to which disease-specific decrements taken from the CARE-HF, MADIT-CRT and RAFT trials were applied. The impact of each intervention on patients' health related quality of life was incorporated as intervention-specific increments, calculated as the difference between baseline and the first follow-up period. These estimates were derived from published sources and individual patient data from the trials included in the manufacturers' systematic review of clinical effectiveness studies. It was assumed

that the health related quality of life benefit from the intervention observed at six months is maintained up to five years and thereafter begins to decrease in a linear manner over a time period of five to ten years. After ten years, the model assumed that a person with a CRT or ICD device will have no additional benefit compared with an identical person receiving OPT. The Assessment Group stated that the submission did not report a systematic review of health-related quality of life studies and the approach differs from that of most previous models (including Buxton et al and Fox et al) where no benefit from the intervention was assumed. In addition, the impact of treatment-related adverse events (such as infection and perioperative complications) on quality of life, which was considered in previous models, was not included in the submission.

6.17 The base case deterministic results are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status, and aetiology (ischaemic or non-ischaemic), but are not presented for the population as a whole or according to the population groups scoped by NICE, and the Assessment Group stated that it is unclear how these results could be aggregated. The base case results are summarised in Table 1 below.

Table 1: Summary of the manufacturer's base case deterministic results

Heart failure severity	**QRS duration**	**ICERs (cost per QALY gained)**
NYHA class I/II	QRS duration < 120ms	ICD vs. OPT: £23,884 to £25,110
	QRS duration 120-149ms	In patients with no LBBB: CRT-D is dominated by ICD ICD vs. OPT: < £17,000. In patients with LBBB:

		CRT-D vs ICD or OPT : <£25,000 (£20,608 to £24,343)
	QRS duration ≥ 150ms	CRT-D in all comparisons: < £28,000
NYHA class III	QRS duration < 120ms	ICD vs. OPT: <£30,000 (£26,923 to £29,402)
	QRS duration 120-149ms	CRT-P vs. OPT: <£20,000. CRT-D vs. CRT-P: £23,900 - £27,400. ICD is either dominated or extendedly dominated with the exception of patients who are non-ischaemic and without LBBB. The ICER for ICD vs. OPT in this group is £19,760 per QALY gained.
	QRS duration ≥ 150ms	CRT-P vs. OPT: < £20,000 CRT- D vs. CRT-P, < £30,000. ICD is either dominated or extendedly dominated.
NYHA class IV	QRS duration < 120ms	No comparative analysis was possible in this patient group, as no patients were identified for this combination.
	QRS duration ≥120ms	CRT-P vs. OPT: <£20,000 CRT-D vs. CRT-P: > £30,000.

6.18 The following scenarios were tested in sensitivity analyses: removal of mortality and health related quality of life effect tapering, use of alternative NYHA based individual patient data results, and increase in device longevity. The base case assumed that treatment effects on mortality or health related quality of life 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. According to the manufacturers' submission, there may be a lower mortality benefit in patients with NYHA class IV compared with NYHA classes I/II/III

for CRT-D. The economic model was run using the estimated all-cause mortality effects based on the grouping of NYHA class IV compared with NYHA class I-III patients. This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups were lower than in the base case. Device longevity was investigated by increasing time to device failure by 10% and this resulted in minimal changes to the cost effectiveness results.

6.19 Probabilistic sensitivity analyses were conducted for 4 subgroups, selected to reflect the baseline characteristics of the MADIT-CRT trial, but no overall population analysis was performed due to the complexity of individual patient level data. Results were presented graphically for 4 patient profiles, that is: men with and without LBBB, and women with and without LBBB. The baseline characteristics of the MADIT-CRT trial was an age of 65-years, NYHA class II, ischemic etiology, QRS >150ms, LVEF between 20 and 25% patients. For these subgroups, CRT-D and OPT showed similar probability of being cost-effective at a threshold of £20,000 per QALY gained.

6.20 The manufacturers stated that caution should be taken not to over-interpret individual subgroups since anomalies may arise as a result of patient level characteristics which have not been accounted for. In addition, the power of this analysis to detect treatment effect modifiers was likely to be low for relatively modest effect modifiers, the trial data on which this analysis is based extends to 7.5 years and treatment effect beyond this point was uncertain. The manufacturers highlighted that the CARE-HF and MADIT II trials reporting extensive long-term follow-up were available were available for consideration. The Assessment Group stated that the manufacturers' submission did not provide any details of the variables included in the probabilistic sensitivity

analyses, such as mean values, distributions and variability of those variables. Credible intervals for mean ICERs of the most cost-effective interventions were also not reported. The Assessment Group therefore noted that it was not clear whether the methods of assessment of parameter uncertainty are appropriate and whether the estimates of variation in the probabilistic sensitivity analyses are appropriate to reflect uncertainty in parameter estimates.

Assessment Group Model

6.21 The Assessment Group adapted the developed by Fox et al. for NICE technology appraisal 120, ‘Cardiac resynchronisation therapy for the treatment of heart failure’. Population 1, that is, people at increased risk of sudden cardiac death from ventricular arrhythmias had not been included in the previous model and the Assessment Group adapted the pathways for this population based on reviews of previous models and expert opinion. The Assessment Group developed a Markov model with monthly cycles over a lifetime time horizon (figure 1) and discounted all future costs and benefits at a rate of 3.5%.

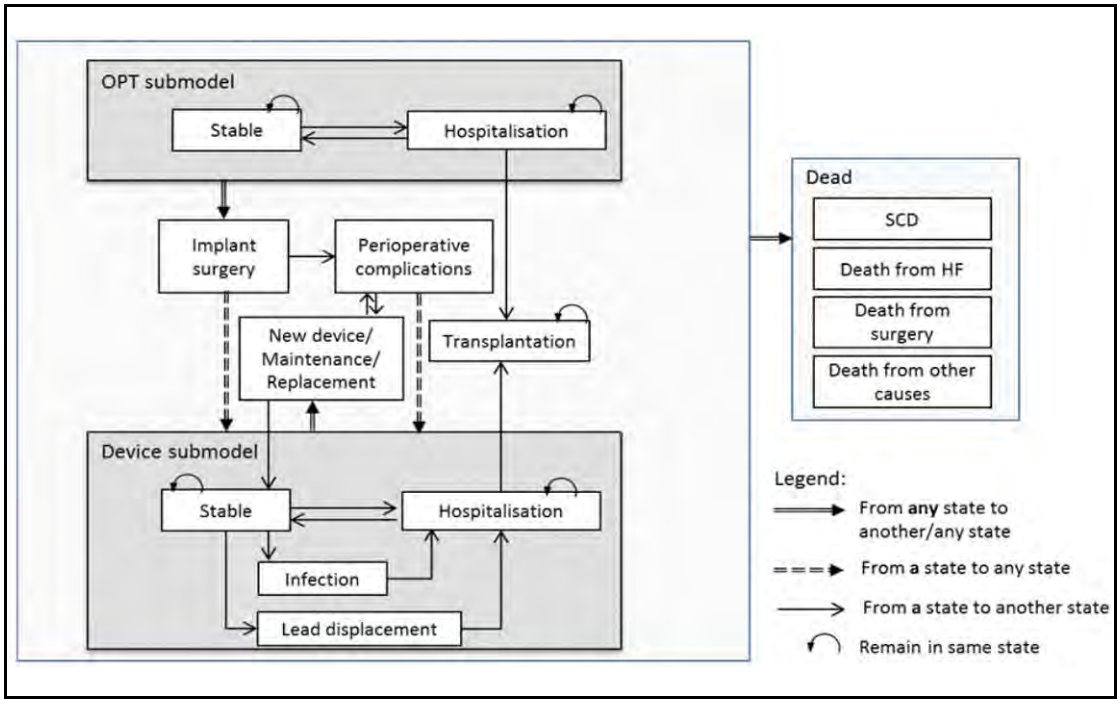


Figure 1: General schematic of the model

6.22 Patients in the comparator arm (managed with medical therapy) enter the model in the stable health state of the OPT sub-model, whereas patients with a device enter the model in the implant surgery state and will typically transition to the stable state in the device sub-model. Patients in a stable health state (either with OPT or with a device) can remain stable, be hospitalised because of heart failure or arrhythmia, or may die from causes other than heart failure of an arrhythmia. In addition, patients in a stable health state with a device may experience device-related adverse events (infection or lead displacement/ failure) or may require maintenance or replacement of their current device. Patients who are hospitalised because of heart failure may be referred for heart transplantation. Patients in any of the live health states (stable, hospitalised, and transplanted) can die from arrhythmia, heart failure, or any other cause (cardiac or non-cardiac).The 3 populations (1, 2 and 3) identified in the scope and described in the

clinical-effectiveness section were modelled. Transitions between health states vary according to the population group and the treatment received. Baseline characteristics (age, sex and, where relevant, proportion in NYHA class) for the modelled populations were based on values reported by relevant clinical trials.

6.23 For population 1, patients in the intervention arm enter the model undergoing ICD implantation surgery and therefore experience a risk of procedure-related death. Those who survive surgery and have a successful implantation can become stable with the device or be hospitalised because of heart failure, perioperative complications, lead displacement, infection, or battery failure. Patients who experience unsuccessful implantations are referred for re-implantation and are subject to the same risks as those who attempt implantation for the first time. Stable ICD patients can further be hospitalised because of heart failure, severe arrhythmia, lead displacement, infection, or battery failure. ICD patients who are hospitalised may continue to be hospitalised, return to the stable state after treatment, or may be referred for heart transplantation (if hospitalised for heart failure). Stable ICD patients are also subject to periodic battery replacement. As with initial implant surgery, and re-implantation, these routine replacement procedures expose the patient to risk of procedure-related death, perioperative complications and unsuccessful implantation.

6.24 In the comparator arm for population 1, patients enter the model in a stable health state where they are treated with OPT in order to prevent major ventricular arrhythmia. Stable OPT patients can remain stable, be hospitalised because of heart failure, or be hospitalised because of major arrhythmia and therefore referred for ICD implantation. Hospitalised patients can return to the stable health state after treatment, be referred for ICD implantation (if hospitalised for major arrhythmia), or be referred for transplantation

(if hospitalised for heart failure). The Assessment Group assumed that patients referred for ICD implantation follow the same pathway as those who enter the model in the ICD arm. The Assessment Group also presented a scenario analysis in which patients in the comparator arm were managed with OPT only, that is, without switching to ICD implantation.

6.25 The Assessment Group assumed that no risk of surgical failure is associated with lead displacements, that, if ICD was not successfully implantated, re-implantation would be attempted in the following cycle with the same risks of adverse events as the first implant. No risk of return to OPT alone was assumed after unsuccessful ICD implantation. The Assessment Group also assumed based on the Fox et al. model, that, people receiving OPT alone who are hospitalised because of a non-fatal arrhythmia receive an ICD and that people who are hospitalised because of heart failure (and had an arrhythmic event) receive an ICD and follow the ICD pathway in the following cycle.

6.26 For population 2, CRT-P in combination with OPT and CRT-D in combination with OPT were compared with each other as well as with OPT alone. For CRT-P, patients enter the model undergoing CRT-P implantation. Patients who survive the procedure with a successful CRT-P implantation may experience perioperative complications, lead displacement, infection, and hospitalisation due to heart failure or severe arrhythmia – those who do not experience any of these events transition to the stable state with CRT-P in combination with OPT. Patients who survive but have unsuccessful CRT-P implantations may return to the OPT stable health state or may be hospitalised because of heart failure or because of severe arrhythmia, and then progress in line with the pathway described below in section 6.28 for people receiving OPT alone. Stable CRT-P patients may be hospitalised if they experience heart failure, lead

displacement, infection, or battery failure. If hospitalised, they may return to a stable state after treatment, remain hospitalised, be referred for an upgrade to CRT-D if they experience serious arrhythmia, or be referred for a heart transplant if they experience worsening heart failure.

6.27 The treatment pathway for patients who received CRT-D is similar to patients who enter the model with CRT-P implantation surgery, except that patients who survive unsuccessful CRT-D implantations are assumed to receive ICD. Those who survive ICD implantation and have a successful implantation can become stable or be hospitalised because of heart failure or severe arrhythmia, perioperative complications, lead displacement, infection, or battery failure. Those who survive with unsuccessful ICD implantations are assumed to receive OPT alone and follow the pathway described below in section 6.28 for people receiving OPT alone.

6.28 For the comparator OPT arm, patients enter the model in a stable health state being treated with OPT in order to prevent heart failure. They may remain stable or be hospitalised because of heart failure or severe arrhythmia. If hospitalised, they may return to the stable health state after treatment, be referred for CRT-P implantation, CRT-D implantation, or transplantation. Patients referred for CRT devices follow a similar pathway to those described above for patients entering the model undergoing CRT-P or CRT-D implantation. The Assessment Group also explored a scenario where patients in the OPT arm were not assumed to receive any device despite failure of treatment with OPT.

6.29 The Assessment Group stated that the assumptions included those previously validated by clinical experts for TA120, as well as some additional assumptions based on clinical advice such as: people who survive unsuccessful CRT-D implantation are assumed to receive ICDs and, for consistency with unsuccessful CRT-P

implantation, patients who survive unsuccessful ICD implantation are assumed to return to receiving OPT alone.

6.30 For population 3, four cohorts were modelled initially receiving CRT-D in combination with OPT, CRT-P in combination with OPT, ICD in combination with OPT or OPT alone, with allowances for subsequent device implants and upgrades. The CRT-D cohort follows a pathway similar to that described for population 2 receiving CRT-D in combination with OPT above (section 6.27), except that if patients who received ICD because of unsuccessful CRT-D implantation, hospitalised because of heart failure are referred for CRT-D re-implantation. The CRT-P cohort follows a similar pathway to that described for population 2 receiving CRT-P in combination with OPT (see section 6.26). In the ICD cohort, patients enter the model undergoing ICD implantation surgery. Those who survive with successful ICD implantations can become stable or be hospitalised because of heart failure, serious arrhythmic event, perioperative complications, lead displacement, infection, or battery failure. Patients hospitalised for heart failure receive a CRT-D implant. Those who survive with unsuccessful ICD implantations are assumed to be managed with OPT alone and follow the OPT pathway described below (section 6.31).

6.31 In the OPT alone cohort, patients may remain stable or be hospitalised because of heart failure or severe arrhythmia. Patients hospitalised for heart failure may return to the stable health state after treatment, be referred for CRT-P implantation, CRT-D implantation, or transplantation. Patients who are hospitalised because of serious arrhythmia are referred for a CRT-D implant. Patients referred for CRT devices follow a similar pathway to those described above for population 3 patients entering the model receiving CRT-P or CRT-D (section 6.30).

6.32 The Assessment Group stated that some assumptions from the model by Fox et al. were maintained in their model, such as patients receiving OPT alone or CRT-P who experience a serious arrhythmic event are assumed to be referred for CRT-D implantation. Patients with an ICD who are hospitalised because of heart failure are also assumed to receive CRT-D and can either become stable with the device or be hospitalised because of heart failure, perioperative complications, lead displacement, or infection, in the following cycle. However, the Assessment Group made some additional assumptions, confirmed by clinical experts, that patients who survive unsuccessful CRT-D implantation would undergo ICD implantations and patients who survive unsuccessful ICD implantation would return to OPT alone.

6.33 In addition, several modelling assumptions were common across the 3 populations. These included: - patients hospitalised because of perioperative complications are assumed to have no risk of surgical death or surgical failure; patients hospitalised because of heart failure while receiving OPT are assumed to have a no risk of remaining hospitalised because of heart failure in the following cycle; only patients who are hospitalised because of heart failure are assumed to be at risk of heart transplant; patients referred to transplantation are assumed to remain in this health state until they die; that the probability of death post-transplant is assumed to be lower than that for non-transplanted patients, except in the first cycle; and that all patients undergoing surgery are assumed to have the same risk of surgery failure. Transition probabilities for moving between health states were based on the estimates of clinical effectiveness from the relevant trials identified in the systematic review.

Population 1

6.34 In population 1, survival data reported in the AVID trial was modelled for the base-case analysis. Survival data from the MADIT II trial was considered representative of a subgroup of patients who had increased risk of ventricular arrhythmia because of previous myocardial infarction. The results from the SCD-HeFT trial were used to inform a subgroup analysis of patients with mild-moderate heart failure. An additional subgroup analysis was conducted for patients with cardiomyopathy using data from a subgroup of patients with non-ischaemic congestive heart failure from SCD-Heft trial. Kaplan-Meier curves for overall survival for the medical therapy arms of the relevant trials were used to derive the baseline mortality risk of patients receiving OPT. Parametric (Weibull) models were fitted to these curves to derive approximate hazard functions and to estimate survival beyond trial follow-up. For patients in the ICD arm of the model, transition probabilities to death were estimated by applying the relative risks estimated in systematic review of clinical effectiveness to the baseline transition probabilities of the OPT arm. For the base case analysis, the pooled relative risk of ICDs compared with OPT 0.75 (95% CI 0.61 to0.93) was used (section 4.4). For primary prevention in the subgroup of patients with remote myocardial infarction, a pooled relative risk from MADIT I and MADIT II of 0.57 (95% CI 0.33 to 0.97) was used (section 4.15). A relative risk of 0.77 (95% CI 0.66 to 0.89) reported in SCD-HeFT was used for patients with mild to moderate heart failure (section 4.27), and a pooled relative risk of 0.74 (95% CI 0.58, 0.93) was used for patients with cardiomyopathy (section 4.19).

6.35 A risk of hospitalisation because of heart failure of 0.0082 (95% CI 0 to 0.0202) per cycle from the MADIT II trial was incorporated in the model for patients at risk of sudden cardiac death being managed with ICD or OPT, assuming that ICDs have no effect on heart failure hospitalisations. As no robust estimation of

hospitalisation rate due to non-fatal arrhythmia for this population was available, the Assessment Group assumed, based on clinical advice, that the baseline probability of a patient receiving OPT to be hospitalised for a non-fatal arrhythmia to be the same as that of patients with heart failure (population 2) (0.0075, 95% CI 0.0002, 0.0148), derived from the number of events in both medical therapy and CRT-P arms of the MIRACLE trial. In addition, the probability of being referred for ICD implantation in patients who are hospitalised because of heart failure while on OPT alone was assumed to be the same as that for patients with heart failure (population 2) in the medical therapy arm of the CARE-HF trial who were referred for CRT-D implantation (0.0018 [95% CI 0 to 0.0059]).

6.36 Adverse events occurring with ICDs were categorised into those occurring at time of implantation (or during the initial in-patient stay) and longer term adverse events. Adverse events at the time of implantation included procedure-related mortality, surgical complications and implant failure while longer term adverse events included lead displacements, infections and device malfunctions and dislodgements. The probability of procedure-related death was taken from the pooled estimate from trials (MADIT II, DEFINITE, DINAMIT, DEBUT and CASH) reporting perioperative deaths related to the implantation procedure; a pooled probability of 0.003 (95% CI 0 to 0.055) per cycle was incorporated in the base case analysis, based on 5 procedure-related deaths among 1449 patients. Because the trials included in the Assessment Group's systematic review did not explicitly report data on implant failure, a probability of 0.011 (95% CI 0.009, 0.013) reported in a systematic review of randomised control trials and observational studies conducted by by Ezekowitz et al. was incorporated in the model. Similarly, probabilities of peri-operative complications of 0.053 (95% CI 0.046 to 0.0.062), of post-operative complications of

0.0012 95% CI 0.0010 to 0.0014) and of infection of 0.0005 (95% CI 0.0004 to 0.0006) were incorporated from this systematic review.

6.37 The distribution of patients by NYHA class was sourced from the baseline distribution of patients in the AVID trial for secondary prevention, and the MADIT II and SCD-HeFT trials for primary prevention of sudden cardiac death and majority of people were in NYHA class I and II (see page 309 of the Assessment Report for further details).

Population 2

6.38 For population 2, for time dependent transition to death, the model accounts for cardiac mortality and for non-cardiac mortality. Baseline time-dependent probabilities of sudden cardiac death and death due to heart failure were derived from survival curves in the medical therapy group of the CARE-HF trial after parameterization (Weibull fitting). For patients receiving devices (CRT-P, CRT-D, or ICD), time-dependent death probabilities were derived by applying device-specific hazard ratio or relative risk to the baseline probabilities. The relative effect on heart failure deaths of CRT-P was obtained from the meta-analysis of the CARE-HF and COMPANION trials which reported a risk ratio of 0.67 for CRT-P compared with medical therapy and for CRT-D compared with medical therapy, a hazard ratio of 0.73 (95% CI 0.47 to 1.11) was included from the COMPANION trial. No effect on sudden cardiac death was assumed in the model (a relative risk of 1) as this estimate was assumed to range between the relative risks reported in the most relevant trials (0.54 in CARE-HF and 1.13 in the COMPANION trial). The relative risk of sudden cardiac death for CRT-D compared to medical therapy was sourced from the COMPANION trial (HR=0.44, 95% CI 0.23 to 0.86). For patients who switched to ICD because of CRT-D implant failure, the relative

risks for sudden cardiac death for ICD compared with medical therapy of 0.44 (95% CI 0.31 to 0.61) was sourced from the SCD-HeFT trial. The SCD-HeFT trial also reported a relative risk of 1.14 (95% CI 0.88 to 1.48) for non-arrhythmic cardiac death which the Assessment Group incorporated as relative risk of death due to heart failure. Non-cardiac death rates were estimated from the 2010 Mortality Statistics for England and Wales and gender proportions of patients with heart failure were estimated based on the 2011 statistics for incidence of heart failure by gender reported by the British Heart Foundation.

6.39 For the hospitalisation baseline risk estimate, a pooled estimate of 0.037 (95% CI 0.025 to 0.049) per cycle was included based on the number of events reported for the medical therapy arm in the relevant trials (CARE-HF, MIRACLE, MUSTIC and COMPANION). The relative risk of hospitalisation because of heart failure with CRT-P compared with OPT alone was estimated to be 0.58 (95% CI 0.35 to 0.96) based on pooling data from the CARE-HF, COMPANION, MIRACLE, and MUSTIC trials. For CRT-D compared with OPT, a relative risk of 0.77 (95% CI 0.63 to 0.93, p=0.008) was included from the COMPANION trial. As per the assumption in the original model by Fox et al., the risk of hospitalisation because of heart failure for patients with ICD was assumed to be the same as for patients receiving OPT.

6.40 The probability of death related to CRT-P implant surgery included in the model was 0.048 (95% CI 0.0015 to 0.0081) per cycle, derived from the number of events reported in the 4 trials included for population 2 and a probability of 0.005 (95% CI 0 to 0.0107) per cycle was derived from the COMPANION trial for CRT-D. Similarly a probability of implant failure of 0.084 (95% CI 0.070, 0.097) per cycle was estimated for patients with CRT-P and of 0.087 (95% CI 0.064 to 0.109) per cycle for patients with CRT-D. The probability of

peri-operative complications related to CRT implantation for both CRT-P and CRT-D (0.1063 was sourced from Fox and colleagues model. For probability of lead displacement, a pooled risk of 0.0037 (95% CI 0.0004 to 0.0071) from 3 trials (CARE-HF, MIRACLE and MUSTIC) was used in the model for both CRT-P and CRT-D. The probability of device-related infections in patients with CRT-P of 0.0006 (95% CI 0 to 0.002) and for patients with CRT-D of 0.0006 (95% CI 0 to 0.0015) per cycle was derived from the trials reporting this outcome.

6.41 According to the treatment pathway (section 6.31) patients receiving OPT can be referred for CRT-P or CRT-D implantation, and patients with CRT-P can be referred for CRT-D following hospitalisation. These probabilities of device upgrade after hospitalisation were derived from the CARE-HF trial. Based on clinical opinion, the Assessment Group assumed that patients would receive ICD only in case of failure to implant CRT-D, and estimated this probability by multiplying the probability of upgrading from OPT to CRT-D by the probability of CRT-D implant. For patients who receive an ICD, the probabilities for ICD-related adverse events are considered to be the same as for those who received ICD in population 1 (see section 6.36).

6.42 The Assessment Group incorporated the same distribution of heart failure patients by NYHA class used in the model by Fox and colleagues. The Assessment Group noted that this was derived based on the distribution of patients per NYHA class at baseline and 90 days in the CARE-HF trial (for further details see page 315 of the Assessment Report).

Population 3

6.43 For population 3, base line mortality was modelled by parametrically (Weibull) fitting Kaplan-Meier curves for all-cause

mortality from the CRT-D arm of the RAFT trial which had the longest average follow-up period of 40 months. The survival data from the MADIT-CRT trial (average follow-up period of 28.8 months) was used in a scenario analysis. The Assessment Group estimated all-cause mortality for patients receiving OPT alone, ICD in combination with OPT, or CRT-P in combination with OPT by applying the hazard ratio or relative risk estimated in the systematic review. No trials for this population compared OPT alone with CRT-D in combination with OPT, therefore a hazard ratio from the COMPANION trial (for population 2) was used assuming that the same relative effect could be expected in this population. Also, since no direct estimates of relative effectiveness of CRT-P and CRT-D were available for this population, and the comparison reported in the COMPANION trial in population 2 was not statistically robust, the Assessment Group assumed the risk of all-cause mortality for patients with CRT-P to be the same as for those with CRT-D with a sensitivity analysis by varying the relative risk between 0.80 to 1.20.

6.44 The Assessment Group derived a baseline risk of hospitalisation because of heart failure of 0.0077, 95% CI 0.0027 to 0.0128) for patients in the CRT-D arm of the model from the number of patients experiencing at least one hospitalisation during the follow-up period in the CONTAK-CD, Piccirillo, and RAFT trials. This estimate was considered conservative as some patients in the trials may have experienced more than one episode of hospitalisation and hence it was likely to underestimate the total number of hospitalisations and consequently resource use. The relative risk for hospitalisation because of heart failure of patients with ICD compared with CRT-D was estimated to be 1.33 (95% CI 1.14 to 1.56) as the reverse of the risk ratio of 0.75 (95% CI 0.64 to 0.88) obtained by pooling data from the CONTAK-CD, Piccirillo, and RAFT trials. Since the COMPANION trial reported no significant differences in

hospitalisations because of heart failure between CRT-P and CRT-D for population 2, the Assessment Group modelled the risk of hospitalisation in CRT-P equal to the risk estimated for the CRT-D arm for population 3. The COMPANION trial also reported a statistically significant difference in heart failure hospital admissions per patient between CRT-D and OPT arms. The relative risk estimated for hospitalisations because of heart failure with OPT compared with CRT-D was used in the model for calculating risk of hospitalisation in the OPT arm of the model.

6.45 The baseline risk of hospitalisation for arrhythmia for the CRT-D arm of the model (0.029, 95% CI 0.015 to 0.042) was derived from trials (MIRACLE, MICACLE ICD II, CONTAK-CD1, and Pinter) reporting the number of patients with CRT-D experiencing at least one episode of ventricular fibrillation. The Assessment Group stated that this approach was likely to underestimate the total number of hospitalisations for arrhythmic events. For the ICD arm the inverse of the relative risk estimated in the meta-analysis was used, that is, 1.11 (95% CI 0.88 to 1.41) (section 4.49). In the absence of any robust evidence, the Assessment Group assumed that the risk for hospitalisation because of arrhythmia for patients managed with OPT alone or with CRT-P was the same as that of patients with CRT-D. Device-related adverse events were poorly reported in the trials included in the systematic review of population 3 and the Assessment Group assumed the same risks of device related adverse events for Population 3 as those for Population 2 (section 6.40).

6.46 The number of patients by NYHA class at baseline was reported in the RAFT trial but no evidence on the effect of the devices on heart failure progression was found; hence the model assumes no effect on patient's distribution by NYHA class. An alternative scenario explored the impact of accounting for the potential benefit of CRT

devices, assuming that 50% of patients with a CRT device improve 1 NYHA class at 6 months of treatment.

6.47 Some parameters were common to all populations; these include age-related mortality (same as in Fox and colleagues' model) , distribution of heart device implants by age (from a report commissioned by the British Cardiovascular Society, the British Heart Foundation and the Cardio & Vascular Coalition), rate of heart transplant surgery (from the MIRACLE trial), mortality associated with transplant surgery (from UK Cardiothoracic Transplant Audit) and in the post-transplant mortality (same as in Fox and colleagues' model). The utility value of patients in stable health states was modelled to vary according to their NYHA class. A utility value of 0.57 was used for hospitalisation and a decrement of 0.05 was applied to health states involving surgery (including initial device implantation, device-related complications and device replacement) and a decrement of 0.1 for infection was also included.. The distribution of patients by NYHA class reported at baseline in the relevant trials for Population 1 were used in combination with utility values by NYHA class by Gohler et al. to estimate a NYHA-class weighted average utility value. The Gohler et al. utility values were 0.855 for NYHA I, 0.771 for NHYA II, 0.673 for NYHA III and 0.532 for NYHA IV. For Population 2, the impact of CRT on health related quality of life over time was captured in the model by changes in the distribution of patients with heart failure by NYHA class derived from the relevant trials. For Population 3, no robust evidence of the effect of devices on heart failure progression was found and CRT and ICD devices were assumed to have no impact on the distribution of patients by NYHA class over time. The model assumed similar utility values for patients with CRT, ICD, or OPT alone for the same NYHA class. In addition, for all population groups, the utility estimates for transplantation were assumed to be similar to those for hospitalised

patients and post-transplanted patients were assumed to have similar utility estimates as NYHA class I patients.

6.48 To estimate resource use, the Assessment Group considered costs of devices, device implantation, device-related complications and maintenance, hospitalisation because of heart failure or severe arrhythmia, medication and heart transplantation. The model estimates resource use associated with each intervention based on event rates and patient transition probabilities among the different health states. Unit costs associated with each resource used were then applied for estimation of total cost per intervention. Estimates of device longevity were also sourced from the joint manufacturers' submission that reported the Kaplan-Meier plots of time to device replacement derived from data submitted to the Central Cardiac Audit Database and estimates of mean time to replacement were derived from the reported survival functions Clinical advice indicated that the longevity might have been overestimated and shorter device longevity was explored in a sensitivity analysis. The mean device cost was estimated to be £3411, £12,293 and £9692 for CRT-P, CRT-D and ICD respectively (see page 332 of the Assessment Report for a complete breakdown of device related total costs used in the model). In the model, patients with heart failure in both the intervention and comparator arms were assumed to receive a combination of drugs according to their NYHA class, and this medical therapy was considered optimal by current standards. The drugs, their daily doses and proportions were included the Assessment Group base-case analysis based on the joint manufacturers submission. Unit costs for the drugs were derived from the British National Formulary (BNF) 61. The cost of OPT management for Population 1 patients without heart failure was assumed to be the same as that for patients in NYHA I. For population 2 and 3, this cost was dependent on the number of patients in each NYHA class.

Table 2: Proportion of drugs (OPT) by NYHA class and associated cost

Drug (mg/day)	Proportion of patients by NYHA class (Cost £)			
	I	II	III	IV
Atorvastatin (10)	20% (0.38)	20% (0.38)	20% (0.38)	20% (0.38)
Simvastatin (20)	55% (0.50)	55% (0.50)	55% (0.50)	55% (0.50)
Warfarin (1)	10% (0.09)	15% (0.13)	25% (0.21)	40% (0.34)
Clopidogrel (75)	15% (0.35)	15% (0.35)	15% (0.35)	15% (0.35)
Ramipril (10)	90% (1.25)	90% (1.25)	90% (1.25)	90% (1.25)
Carvedilol (25)	85% (1.37)	85% (1.37)	75% (1.21)	70% (1.13)
Spironolactone (25)	0% (0)	30% (0.43)	30% (0.43)	30% (0.43)
Digoxin (125)[a]	5% (0.05)	25% (0.25)	25% (0.25)	25% (0.25)
Furosemide (60)	75% (1.8)	80% (1.92)	90% (2.16)	95% (2.28)
Eplerenone (25)	0% (0)	30% (12.82)	30% (12.82)	30% (12.82)
Total cost (£)	5.78	19.39	19.56	19.73
[a] Dosing measured in µg per day.				

Results of Assessment Group's economic analysis and sensitivity analysis

Population 1

6.49 In the base-case analysis, in a mixed gender cohort of 65 year old patients, ICD in combination with OPT arm were associated with incremental QALYs of 0.80, incremental costs of £15,492 and an ICER of £19,479 per QALY gained compared with OPT alone. These results presented by age group indicated that the ICER increases with age, ranging from £17,083 per QALY gained at 30 years to £28,211 per QALY gained at 80 years. The Assessment Group also presented results for a mixed age and gender cohort, using the distribution of ICD implants by age in the UK as proxy for the distribution of patients at increased risk of sudden cardiac death due to ventricular arrhythmia. The results indicated incremental

QALYs of 0.7, incremental costs of £15,279 and an ICER of £24,967 per QALY gained for ICD in combination with OPT compared with OPT alone.

6.50 The Assessment Group also presented subgroup analyses for ICD in combination with OPT compared with OPT alone. First, for patients with remote myocardial infarction, using MADIT II all-cause mortality for a cohort of 64-year old patients, the ICER was £14,231 per QALY gained. Second, for patients with mild-moderate heart failure, the ICER was £29,756 per QALY gained and third, for patients with cardiomyopathy, the ICER was £26,028 per QALY gained. Please refer to section 6.34 for details of the estimates incorporated in these analyses.

6.51 The Assessment Group conducted univariate sensitivity analyses on the key inputs in the model. The inputs which had most impact were using a time horizon of 3 years rather than a lifetime time horizon which increased the ICER for ICD in combination with OPT compared with OPT alone to £141,235 per QALY gained; using upper limit of 95% CI for risk ratio of all cause mortality for ICDs compared to OPT of 0.93 which resulted in an ICER of £78,268 per QALY gained; and increasing the risk of surgery-related death to 0.055 which resulted in an ICER of £32, 605 per QALY gained (see page 339 of the Assessment Report for further details).

6.52 The Assessment Group also conducted a scenario analysis in an appendix to the Assessment Report where it was assumed that in the OPT alone arm, patients would not receive an ICD if they were not responding to OPT alone. This resulted in an incremental QALY of 1.16, incremental cost of £26,294 and an ICER of £22,710 for ICD in combination with OPT compared with OPT alone. In another scenario analysis, incorporating higher device related costs, that is using the upper limit of the 95% CI for device-related costs resulted in an ICER of £37,832 per QALY gained. Other scenario analyses

did not have a substantial impact on the ICER, please see page 341 and 342 of the Assessment Report.

6.53 The Assessment Group also performed a probabilistic sensitivity analysis for the base case to estimate the impact of joint parameter uncertainty on the model's cost-effectiveness results. The resulting probabilistic mean ICER was £20,479 per QALY gained. The addition of ICD to OPT for secondary prevention of sudden cardiac death has a 51% probability of being cost-effective at £20,000 per QALY gained, and a probability of 82% at £30,000 per QALY gained.

Population 2

6.54 For the base case analysis, the Assessment Group modelled a 70 year-old mixed-gender cohort of patients with heart failure. The comparison of CRT-P in combination with OPT with OPT alone resulted in incremental QALYs of 0.69, incremental costs of £18,845 and an ICER of £27,584 per QALY gained. The comparison of CRT-D in with CRT-P (both in combination with OPT) resulted in incremental QALYs of 0.41, incremental costs of £11,703 and an ICER of £28,420 per QALY gained. As for population 1, these results presented by age group indicated that the ICER increases with age, estimated at approximately £32,000 per QALY gained for both comparisons at 80 years. The Assessment Group also presented an ICERs for a mixed age and gender cohort which were estimated as £28,928 per QALY gained for the comparison of CRT-P with OPT and £30,321 per QALY gained for the comparison of CRT-D with CRT-P.

6.55 The Assessment Group conducted a scenario analysis reported in an addendum to the Assessment Report where it was assumed that in the OPT alone arm, patients would not receive any device even if they were not responding to OPT alone. This resulted in a

reduction in costs in the OPT alone arm from £7615 to £7300, resulting an ICER of £27,644 per QALY gained for CRT-P in combination with OPT compared with OPT alone and an ICER of £28,429 per QALY gained for CRT-D compared with CRT-P (both in combination with OPT). In other scenario analyses conducted by the Assessment Group, for the comparison of CRT-P with OPT alone, varying device related costs had the most impact on the ICER with estimates ranging from £20,977 to £48,486 per QALY gained and varying the utility assumptions reduced the ICER to £22,892 per QALY gained. For the comparison of CRT-D with CRT-P, incorporating higher device related costs resulted in a higher ICER of £61,967 per QALY gained and assuming a shorter device lifetime resulted in an ICER of £34,416 per QALY gained.

6.56 The Assessment Group conducted a range of sensitivity analyses. For the comparison of CRT-P with OPT alone, the inputs which had most impact were: using a lower risk of hospitalisation for non-fatal arrhythmia with CRT-P of 0.0002, instead of 0.0075, which reduced the ICER to £15,780 per QALY gained; assuming a greater relative risk of heart failure death with CRT-P of 0.88, rather than, 0.67, which increased the ICER to £36,019 per QALY gained; and assuming a greater relative risk of heart failure death with CRT-D of 1,11, rather than 0.73, which increased the ICER to £34,720 per QALY gained. Sensitivity analyses on inputs for the comparison of CRT-D with CRT-P had substantial impacts on the ICER and these are summarised in table 5, appendix C.

6.57 The Assessment Group conducted scenario analyses to assess the effect of change in assumption in the model on the base-case ICERs. Assuming shorter lifetime of devices as used in the previous model by Fox and colleagues results in slightly higher cost for all strategies with minimal effect on the QALYs and the overall effect was that both OPT and CRT-P strategies are either

dominated or extendedly dominated by CRT-D which is associated with a lower ICER of £23,690 per QALY gained compared to ICD. Other scenarios like use of utility values as in the Fox and colleagues' and assuming CRT devices improve NYHA class by 1 in 50% of patients at 6 months, have no substantial effect on the ICERs. Varying device cost to their upper and lower limits of 95% of confidence interval resulted in the ICERs associated with CRT-D ranging from £13,829 to £60,864 per QALY gained.

6.58 The Assessment Group's resulting probabilistic mean ICER for CRT-P compared with OPT alone was £27,434 per QALY gained while the probabilistic mean ICER for CRT-D compared with CRT-P was £27,899 per QALY gained. At £20,000 per QALY gained, OPT alone has the highest probability of being cost-effective (83%) while at £30,000 per QALY gained, CRT-D and CRT-P have 46% and 31% probability of being cost-effective, respectively compared to OPT alone (23%).

Population 3

6.59 CRT-P was associated in the model with a marginally higher cost and slightly fewer QALYs than CRT-D, and was therefore dominated by CRT-D. When compared with the next most cost-effective option, that is, OPT alone, the ICER was £41,414 per QALY gained and CRT-P was therefore extendedly dominated by CRT-D compared with OPT alone as this was associated with a smaller ICER of £35,193 per QALY gained. Therefore, the base-case analysis estimated incremental QALYs of 0.10, incremental costs of £287 and an ICER of £2824 for OPT alone compared with ICD therapy; and incremental QALYs of 0.31, incremental costs of £10,906 and an ICER of £35,193 per QALY gained for CRT-D compared with OPT only.

6.60 The Assessment Group's scenario analysis in which it was assumed that patients in the OPT arm cannot receive ICD or CRT devices even if they were not responding to OPT alone, resulted in a reduction in estimated costs by £30,580 and in estimated benefits by 0.88 QALYs compared with the base case OPT only arm so that OPT alone became the least costly and least effective strategy. As before, CRT-P was extendedly dominated by CRT-D, and ICD was also extendedly dominated by CRT-D. Therefore, for the relevant comparison of CRT-D with OPT alone, incremental costs were £41,485, incremental QALYs of 1.18 and the ICER was £35,010 per QALY gained. The Assessment Group stated that in this scenario analysis, though incremental costs of the interventions compared with OPT had substantially increased, a corresponding gain in incremental QALYs had resulted in similar ICERs as in the base case analyses.

6.61 In another scenario analysis, the Assessment Group included estimates of all-cause mortality reported for men in the CRT-D arm, and the respective hazard ratio for ICD for the whole population, from the MADIT-CRT trial (1.00, 95% CI 0.69, 1.44). The results showed that CRT-P and CRT-D are less effective and more costly than ICD and hence both CRT strategies were extendedly dominated by ICD compared with OPT alone. Therefore, the results obtained with MADIT-CRT data indicate that ICD as the most cost-effective strategy, with an ICER of £154 per QALY gained compared with OPT alone.

6.62 The Assessment Group reported results from sensitivity analyses only for those changes when variation between the 95% CI limits caused a change of more than £20,000 per QALY gained in the ICER. These are summarised in the table 9, appendix C for the relevant comparisons. Scenario analyses were conducted and these are described in table 10 of the appendix C. The ICERs

remained similar to the base case when it was assumed that 50% of patients with a CRT device would improve 1 NYHA class at 6 months of treatment and also when alternative utility estimates used by Fox et al. were incorporated.

6.63 The Assessment Group conducted probabilistic sensitivity analyses and these results are consistent with the deterministic results. At £20,000 per QALY gained, the probability of OPT alone being cost-effective was 57%, 37% for ICD, and approximately 3% for CRT-D and for CRT-P. At £30,000 per QALY gained, OPT alone, ICD, CRT-D, and CRT-P have 44%, 31%, 15%, and 10% probability of being cost-effective respectively.

7 Equalities issues

7.1 Consultees highlighted during scoping consultation and in the evidence submitted that there were significant differences in access to device therapy across the UK.

8 Innovation

8.1 No claims for innovation were presented. However, consultees commented that ICD and CRT devices had revolutionised the treatment of arrhythmias and heart failure.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Chronic heart failure. NICE clinical guideline 108(2010). Available from www.nice.org.uk/guidance/CG108
- Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120(2007). Available from www.nice.org.uk/guidance/TA120

Recommendations:

1.1 Cardiac resynchronisation therapy with a pacing device (CRT-P) is recommended as a treatment option for people with heart failure who fulfil all the following criteria.

- They are currently experiencing or have recently experienced New York Heart Association (NYHA) class III–IV symptoms.
- They are in sinus rhythm:
  - **either** with a QRS duration of 150 ms or longer estimated by standard electrocardiogram (ECG)
  - **or** with a QRS duration of 120–149 ms 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.

1.2 Cardiac resynchronisation therapy with a defibrillator device (CRT-D) may be considered for people who fulfil the criteria for implantation of a CRT-P device in section 1.1 and who also separately fulfil the criteria for the use of an ICD device as recommended in NICE technology appraisal guidance 95.

- Implantable cardioverter defibrillators for arrhythmias. NICE technology appraisal guidance 95 (2006). Available from www.nice.org.uk/guidance/TA95

Recommendations

1.1 ICDs are recommended for patients in the following categories.

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

- having survived a cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF)
- spontaneous sustained VT causing syncope or significant haemodynamic compromise
- sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF of less than 35%) (no worse than class III of the New York Heart Association functional classification of heart failure).
- 1.1.2 'Primary prevention', that is, for patients who have:
- a history of previous (more than 4 weeks) myocardial infarction (MI)

  either

  - left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure), **and**
  - non-sustained VT on Holter (24-hour electrocardiogram [ECG]) monitoring, **and**
  - inducible VT on electrophysiological (EP) testing

  or

  - left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure) **and**
  - QRS duration of equal to or more than 120 milliseconds
- a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia (ARVD), or have undergone surgical repair of congenital heart disease.

NICE pathways

- There is a NICE pathway on chronic heart failure, which is available from http://pathways.nice.org.uk/pathways/chronic-heart-failure

Appendix B: Summary result of the systematic review and meta-analysis by the Assessment Group

People at risk of SCD as a result of ventricular arrhythmias (population 1)

Population	No. of included trial	Event rate (n/N)		Relative effect (relative risk or hazard ratio)	95% CI	Reference
		ICDs	Medical therapy			
All-cause mortality						
Population 1 overall	13 +1 pilot study	819/4200	1251/4935	0.81	0.71 to 0.93	Figure 4 (page 86 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	4 trials+1 pilot study	199/981	311/1068	0.75	0.61 to 0.93	Figure 4 (page 86 of AR)
Subgroup-people with a recent myocardial	2	178/777	175/795	1.04	0.86 to 1.25	Figure 4 (page

infarction (primary prevention)						86 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	120/837	136/591	0.57	0.33 to 0.97	Figure 4 (page 86 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	3	38/330	49/335	0.77	0.52 to 1.15	Figure 4 (page 86 of AR)
Subgroup-people scheduled for CABG surgery	1	102/446	96/454	1.08	0.85 to 1.38	Figure 4 (page 86 of AR)
Subgroup-people with mild to moderate HF	1	182/829	484/1692	0.77	0.66 to 0.89	Figure 4 (page 86 of AR)
Total cardiac deaths						
Population 1 overall	10	567/3825	845/4478	0.80	0.69 to 0.92	Figure 5 (page 88 of AR)
Subgroup of people with cardiac arrest	2	130/835	177/840	0.74	0.61 to 0.91	Figure 5 (page

(secondary prevention)						88 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	141/777	148/795	0.97	0.79 to 1.20	Figure 5 (page 88 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	90/837	107/591	0.59	0.42 to 0.83	Figure 5 (page 88 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	2	8/101	5/106	2.03	0.17 to 23.62	Figure 5 (page 88 of AR)
Subgroup-people scheduled for CABG surgery	1	76/446	79/454	0.98	0.74 to 1.30	Figure 5 (page 88 of AR)
Subgroup-people with mild to moderate HF	1	122/829	329/1692	0.76	0.63 to 0.92	Figure 5 (page 88 of AR)
Sudden cardiac deaths/arrhythmic deaths						

Population 1 overall	13 +1 pilot study	194/4200	540/4935	0.45	0.38 to 0.53	Figure 6 (page 94 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	4 trials+1 pilot study	67/981	167/1068	0.49	0.34 to 0.69	Figure 6 (page 94 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	39/777	89/795	0.45	0.31 to 0.64	Figure 6 (page 94 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	31/837	62/591	0.36	0.23 to 0.55	Figure 6 (page 94 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	3	4/330	16/335	0.26	0.09 to 0.77	Figure 6 (page 94 of AR)
Subgroup-people scheduled for CABG surgery	1	15/446	28/454	0.55	0.30 to 1.01	Figure 6 (page 94 of AR)

Subgroup-people with mild to moderate HF	1	38/829	178/1692	0.44	0.31 to 0.61	Figure 6 (page 94 of AR)
Non-arrhythmic cardiac deaths						
Population 1 overall	11	382/4054	377/4707	1.21	1.01 to 1.45	Figure 7(page 97 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	2	76/835	79/840	0.97	0.72 to 1.31	Figure 7(page 97 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	102/777	59/795	1.77	1.30 to 2.44	Figure 7(page 97 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	50/837	34/591	0.95	0.41 to 2.18	Figure 7(page 97 of AR)
Subgroup- people with cardiomyopathy	3	16/330	14/335	1.13	0.42 to 3.03	Figure 7(page 97 of AR)

(primary prevention)						
Subgroup-people scheduled for CABG surgery	1	57/446	46/454	1.26	0.87 to 1.82	Figure 7(page 97 of AR)
Subgroup-people with mild to moderate HF	1	81/829	145/1692	1.14	0.88 to 1.48	Figure 7(page 97 of AR)
Non-cardiac deaths						
Population 1 overall	10	171/3825	216/4478	1.02	0.83 to 1.25	Figure 8 (page 101 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	2	33/835	43/840	0.79	0.45 to 1.37	Figure 8 (page 101 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	37/777	27/795	1.39	1.86 to 2.27	Figure 8 (page 101 of AR)

Subgroup-people with remote myocardial infarction (primary prevention)	2	26/837	18/591	1.06	0.58 to 1.95	Figure 8 (page 101 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	2	2/101	4/106	0.65	0.13 to 3.29	Figure 8 (page 101 of AR)
Subgroup-people scheduled for CABG surgery	1	25/446	17/454	1.50	0.82 to 2.73	Figure 8 (page 101 of AR)
Subgroup-people with mild to moderate HF	1	48/829	107/1692	0.92	0.66 to 1.27	Figure 8 (page 101 of AR)
Hospitalisations						
Subgroup of people with cardiac arrest (secondary prevention)						
AVID trial (N=1011)	- at 1 year	59.5%	55.6%		p value; 0.04	Table 24 (page 106 of AR)
	- at 2 years	74.8%	64.7%			Table 24 (page

						106 of AR)
	- at 3 years	83.3%	75.5%			Table 24 (page 106 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)						
Hospitalisation due to heart failure (MADIT II)	Hospitalisation due to heart failure, n (%)	148 (19.9)	73 (14.9)			Table 24 (page 106 of AR)
	Patients hospitalised, per 1000 months of active follow-up	11.3	9.4		p value; 0.09	Table 24 (page 106 of AR)

People with heart failure as a result of LVSD and cardiac dyssynchrony (population 2)

Comparison	No. of included trial	Event rate (n/N)		Relative effect (relative risk or hazard ratio)	95% CI	Reference
		Intervention	Comparator			
All-cause mortality						
CRT-P vs. medical therapy	4	247/1312	247/995	0.75	0.58 to 0.96	Figure 10 (page 157 of AR)
CRT-D vs. medical therapy	1	71/595	59/308	0.64	0.48 to 0.86	Table 34 (page 156 of AR)
CRT-P vs. CRT-D	1	131/617	105/595	1.20	0.96 to 1.52	Table 34 (page 156 of AR)
Total cardiac deaths						

CRT-P vs. medical therapy	MUSTIC	2/29	0/29	7.00	0.37 to 132.56	Table 35 (page 158 of AR)
	COMPANION	109/617	58/308	0.94	0.70 to 1.25	Table 35 (page 158 of AR)
CRT-D vs. medical therapy	COMPANION	76/595	58/308	0.68	0.50 to 0.93	Table 35 (page 158 of AR)
CRT-P vs. CRT-D	COMPANION	109/617	76/595	1.38	1.06 to 1.81	Table 35 (page 158 of AR)
Heart failure deaths						
CRT-P vs. medical therapy	2	91/1026	98/712	0.67	0.51 to 0.88	Figure 11 (page 161)
CRT-D vs. medical therapy	1	52/595	34/308	0.73	0.47 to 1.11	Table 36 (page 160)
CRT-P vs. CRT-D	1	53/617	52/595	0.98	0.68 to 1.42	Table 36 (page 160)

Sudden cardiac death						
CRT-P vs. medical therapy	3	82/1084	72/770	0.97	0.44 to 2.44	Figure 12 (page 160 of AR)
CRT-D vs. medical therapy	1	17/595	18/308	0.44	0.23 to 0.86	Table 37 (page 163)
CRT-P vs. CRT-D	1	48/617	17/595	2.72	1.58 to 4.68	Table 37 (page 163)
Number of people hospitalised due to heart failure						
CRT-P vs. medical therapy	4	272/1283	288/966	0.61	0.44 to 0.83	Figure 13 (page 167 of AR)
CRT-D vs. medical therapy	1	166/595	112/308	0.77	0.63 to 0.93	Table 39 (page 166 of AR)
CRT-P vs. CRT-D	1	179/617	166/595	NR	Not significant	(page 165 of AR)

Number of hospitalisations due to heart failure						
CRT-P vs. medical therapy	4			0.58	0.35 to 0.96	Figure 14 (page 168 of AR)
Worsening heart failure						
CRT-P vs. medical therapy	3	204/695	288/688	0.71	0.63 to 0.80	Figure 15 (page 170 of AR)
Participants with improvement in ≥1 NYHA class						
CRT-P vs. medical therapy	3	696/1109	301/799	1.68	1.52 to 1.86	Figure 16 (page 175 of AR)
CRT-D vs. medical therapy	1	283/497	76/199	2.14	2.14 to 1.53	Table 43 (page 174 of AR)
CRT-P vs. CRT-D	1	298/489	283/497	0.93	0.84 to 1.04	Table 43 (page 174 of AR)

Change in LVEF (Median change from base line)						
CRT-P vs. medical therapy	1	: +4.6,	-0.2		p<0.001	Figure 16 (page 175 of AR)
Change in 6-minute walk distance at 6 months						
CRT-P vs. medical therapy	3			Mean difference 38.14	21.74 to 54.54	Figure 17 (page 176 of AR)
CRT-D vs. medical therapy	1	46	1		<0.001	Table 44 (page 177 of AR)
CRT-P vs. CRT-D	1	40	46	MD -6.0	-19.87 to 7.87	Table 44 (page 177 of AR)

People with both conditions (population 3)

Population	No. of included trial	Event rate (n/N)		Relative effect (relative risk or hazard ratio)	95% CI	Reference
		CRT-D	ICD			
All-cause mortality						
Population 3 overall	9	302/2722	327/2342	0.84	0.73 to 0.96	Figure 19 (page 208 of AR)
Subgroup of NYHA class II	3	262/2086	291/1736	0.82	0.71 to 0.96	Figure 19 (page 208 of AR)
Subgroup of NYHA class III	5	40/638	136/591	0.95	0.60 to 1.50	Figure 19 (page 208 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 19 (page 208 of AR)

Total cardiac deaths						
Population 3 overall	7	145/1446	177/1429	0.82	0.67 to 1.00	Figure 20 (page 209 of AR)
Subgroup of NYHA class II	2	132/979	164/1005	0.81	0.66 to 1.01	Figure 20 (page 209 of AR
Subgroup of NYHA class III	4	13/451	13/409	0.89	0.40 to 1.96	Figure 20 (page 209 of AR
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 20 (page 209 of AR
Heart failure deaths						
Population 3 overall	4	6/433	10/446	0.64	0.18 to 2.22	Figure 21 (page 210 of AR)
Subgroup of NYHA class II	1	0/85	0/101	Not estimable		Figure 21 (page 210 of AR)

Subgroup of NYHA class III	2	6/332	10/330	0.64	0.18 to 2.22	Figure 21 (page 210 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 21 (page 210 of AR)
Sudden cardiac deaths						
Population 3 overall	6	6/703	4/671	1.45	0.43 to 4.92	Figure 22 (page 211 of AR)
Subgroup of NYHA class II	1	2/85	1/101	2.38	0.22 to 25.76	Figure 22 (page 211 of AR)
Subgroup of NYHA class III	4	4/602	3/555	1.22	0.29 to 5.04	Figure 22 (page 211 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 22 (page 211 of AR)
Arrhythmias						

Population 3 overall	4	104/553	118/564	0.90	0.71 to 1.14	Figure 24 (page 215 of AR)
Subgroup of NYHA class II	1	19/85	26/101	0.87	0.52 to 1.46	Figure 24 (page 215 of AR)
Subgroup of NYHA class III	3	85/468	92/463	0.91	0.70 to 1.18	Figure 24 (page 215 of AR)
Change in NYHA class (mean difference)						
Population 3 overall	3			Mean difference: -0.19	-0.34 to -0.05	Figure 25 (page 218 of AR)
Subgroup of NYHA class II	1	-0.18	0.01	-0.19	-0.37 to -0.01	Figure 25 (page 218 of AR)
Subgroup of NYHA class III	2			-0.20	-0.43 to 0.03	Figure 25 (page 218 of AR)
Proportion of people with improvement in NYHA class						

Population 3 overall	3	93/201	61/211	1.81	0.91 to 3.60	Figure 26 (page 218 of AR)
Subgroup of NYHA class III	2	80/185	60/196	1.44	0.87 to 2.38	Figure 26 (page 218 of AR)
Subgroup of NYHA class IV	1	13/16	1/15	12.19	1.81to 82.15	Figure 26 (page 218 of AR)
Change in LVEF (mean difference)						
Population 3 overall	8			2.15	0.45 to 3.86	Figure 27 (page 221 of AR)
Subgroup of NYHA class II	2			5.05	0.23 to 9.87	Figure 27 (page 221 of AR)
Subgroup of NYHA class III	5			0.79	-0.58 to 2.16	Figure 27 (page 221 of AR)
Subgroup of NYHA class IV	1	28	22	6.00	1.50 to 10.50	Figure 27 (page 221 of AR)

Change in peak VO_2 (mean difference)						
Population 3 overall	5			0.75	0.23 to 1.27	Figure 28 (page 222 of AR)
Subgroup of NYHA class II	1	0.5	0.2	0.30	-0.75 to 1.35	Figure 28 (page 222 of AR)
Subgroup of NYHA class III	4			0.84	-0.23 to 1.46	Figure 28 (page 222 of AR)
Change in 6-minute walk distance (mean difference)						
Population 3 overall	6			14.53	2.94 to 26.11	Figure 29 (page 222 of AR)
Subgroup of NYHA class II	1	38	33	5.00	-26.33 to 36.33	Figure 29 (page 222 of AR)
Subgroup of NYHA class III	5			16.04	3.56 to 28.51	Figure 29 (page 222 of AR)

Appendix C: Summary results of the cost-effectiveness analysis by the Assessment Group

Population 1

Table 1: Base-case result population 1

Description	ICD+OPT		OPT		
	Costs (£)	QALYs	Costs	QALYs	ICER (£/QALY)
Base-case ICD for secondary prevention of SCD Mixed gender cohort of 65-year old patients (all cause mortality from AVID trial)	31,382	6.75	15,890	5.95	**19,479**
Mixed age cohort (distribution of ICD implants by age used for the age distribution of patients	31,838	6.91	16,559	6.17	24,967
ICD for primary prevention of SCD in patients with remote MI using MADIT II all-cause mortality for a cohort of 64-year old patients	31,583	6.35	14,783	5.17	14,231
ICD for primary prevention of SCD in patients with mild-moderate heart failure (60 year-old patients with mild-moderate heart failure with indication for an ICD, all-cause mortality of the placebo arm, the RR for ICD of 0.77 (95% CI 0.66, 0.89), and the distribution of patients by NYHA class from the SCD-HeF)	32,416	6.28	17,760	5.79	29,756
ICD for primary prevention of SCD in patients with cardiomyopathy 60 year-old patients with cardiomyopathy, a pooled RR of 0.74 (95% CI 0.58, 0.93) from the non-ischaemic subgroup of SCD-HeFT, AMIOVIRT, CAT, and DEFINITE. The SCD-HeFT distribution of patients by NYHA	40,218	8.42	24,845	7.83	26,028

Table 2 Univariate sensitivity analysis results for Population 1

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALY	ICER (£/QALY gained)
Base case	-	-	15,492	0.80	19,479
Survival and HRs					
All-cause mortality HR (ICD)	0.75	0.61	17,126	1.37	12,480
		0.93	13,772	0.18	78,268
Event probabilities					
Risk of surgery related death (ICD)	0.003	0	15,491	0.82	18,950
		0.055	15,507	0.48	32,605
Device lifetime ln(λ) and γ	-15.78 1.94 (~ 8 years)	-16.182 1.889 (~13 years)	13,158	0.80	16,456
		-15.385 1.996 (~5 years)	19,467	0.79	24,706

Table 3: Scenario analyses population1

		ICD+OPT		OPT		
Scenario	**Description**	**Costs (£)**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
Base-case	ICD for secondary prevention of SCD	31,382	6.75	15,890	5.95	19,479
OPT only for comparator arm	patients in the comparator arm being managed with OPT only (no upgrades to a device)	31,382	6.75	5,088	5.59	**22,710**
Alternative assumption for risk of hospitalisation due to arrhythmia	risk of hospitalisation due to arrhythmia was assumed to be 0.032 for both the arms	37,120	6.74	29,759	6.34	18,185
Alternative assumption about utility	a mean utility estimate of 0.75 irrespective of NYHA class and treatment arm					22,372
Alternative assumption about device related cost*	Upper limit of 95% CI					37,832
	lower limit of 95% CI					16,888
* include cost associated with implantation, perioperative complications, treatment of lead displacement, infection, and device replacement						

Population 2

Table 4. Base case and OPT only scenario analysis results for Population 2

Strategy	Cost (£)	QALYs	ICER (£/QALY gained)
Base case (*vs. next best option* [b])			
OPT	7,615	3.48	-
CRT-P + OPT	26,460	4.17	27,584
CRT-D + OPT	38,163	4.58	28,420
OPT only scenario (*vs. next best option* [b])			
OPT only	7,300	3.47	-
CRT-P + OPT	26,430	4.17	27,644
CRT-D + OPT	38,162	4.58	28,429

[b] Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated;

Table 5: Population 2 subgroup, univariate, scenario and probabilistic analyses for CRT-P+ vs. OPT

CRTP+OPT vs. OPT		Intervention		Comparator		
Description		**Costs (£)**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
Base-case (mixed gender cohort of 70-year old patients)		26,460	4.17	7,615	3.48	27,584
Mixed age cohort (using distribution of patients with heart failure by age group reported in literature)		28,016	4.47	8,218	3.75	28,928
Risk of hospitalisation for non-fatal arrhythmia with CRT-P (0.0075)	0.0002					15,780
	0.0148					31,978
RR of HF death with CRT-P(0.67)	0.51					23,307
	0.88					36,019
RR of HF death with CRT-D(0.73)	0.47					23,522
	1.11					34,720
RR of SCD with CRT-P (1)	0.54					19,825
	1.13					30,925
Scenario analyses						
OPT only scenario		26,430	4.17	7,300	3.47	27,644
Shorter devices' lifetime (using the device lifetime estimates in Fox and colleagues		28,555	4.15			31,334
Alternative utility assumption (utility estimates used by Fox and colleagues)		26,460	4.21			22,892
Alternative assumption about device related cost*	Upper limit of 95% CI					48,486

	lower limit of 95% CI					20,977
Probabilistic sensitivity analysis						
PSA was performed to by 10,000 iterations		25,874	4.14	7,604	3.48	27,434***
* include cost associated with implantation, perioperative complications, treatment of lead displacement, infection, and device replacement ** supplement of the Assessment Report *** Interquartile range (16,314; 47,527) Blank cells indicate that values have not been reported in the Assessment Report						

Table 6: Population 2 subgroup, univariate, scenario and probabilistic analyses for CRT-D+OPT vs. CRT-P+OPT

		CRT-D		**CRT-P**		
Description		**Costs (£)**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
Base-case (mixed gender cohort of 70-year old patients)		38,163	4.58	26,460	4.17	28,420
Mixed age cohort (using distribution of patients with heart failure by age group reported in literature)		39,932	4.88	28,016	4.47	30,321
Scenario analyses						
Shorter devices' lifetime (using the device lifetime estimates in Fox and colleagues		42,627	4.56	28,555	4.15	34,416
Alternative utility assumption (utility estimates used by Fox and colleagues)		38,163	4.63	26,460	4.21	27,893
Alternative assumption about device related cost*	Upper limit of 95% CI					61,967
	lower limit of 95% CI					28,090
Probabilistic sensitivity analysis						
PSA was performed to by 10,000 iterations		38,156	4.56	25,874	4.14	27,899 ***

Univariate sensitivity analysis				
Parameter (base-case value)	**Value in sensitivity analysis**	**∆Costs (£)**	**∆QALYs**	**ICER (£/QALY)**
RR of HF death with CRT-D (0.72)	0.47	13,754	0.78	17,602
	1.11	9,545	0.01	793,839
RR of SCD with CRT-P (1)	0.54	10,063	0.06	169,196
	1.13	12,108	0.50	24,250
RR of SCD with CRT-D (0.44)	0.23	12,817	0.62	20,180
	0.86	9,912	0.08	129,220
Device lifetime (CRT-D), (~7y)	~13yrs	8,608	0.43	20,238
	~4yrs	17,811	0.38	46,640
RR of HF death with CRT-P(0.67)	0.51	10,966	0.25	43,231
	0.88	12,563	0.60	21,042
Risk of hospitalisation for non-fatal arrhythmia with CRT-P(0.0075)	0.0002	21,857	0.54	40,450
	0.0148	6,335	0.34	18,707
Baseline mortality due to HF, ln(λ), γ (-6.115, 1.223)	-6.253, 1.180	12,546	0.52	24,157
	-5.977, 1.265	10,864	0.31	35,220
Baseline mortality due to SCD, ln(λ), γ, (-6.069, 1.140)	-6.173, 1.107	11,460	0.33	34,318
	-5.964, 1.173	11,924	0.49	24,316

Population 3

Table 8: Population 3 Base case and OPT only scenario

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
Base case (*vs. next best option* [b])				
ICD + OPT	39,719	7.45	5.57	-
OPT	40,006	7.59	5.67	2,824
CRT-P + OPT	51,202	7.96	5.94	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	35,193
OPT only scenario (*vs. next best option* [b])				
OPT only	9,426	6.41	4.79	-

ICD + OPT	39,719	7.45	5.57	Extendedly dominated
CRT-P + OPT	51,202	7.96	5.94	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	35,010

Table 9 Population 3 univariate sensitivity analysis

Parameter	**Base case value**	**DSA value**	**Incremental Cost (£)**	**Incremental QALYs**	**ICER (£/QALY gained)**
Univariate sensitivity analysis results for CRT-D + OPT vs OPT					
Base case	-	-	10,906	0.31	35,193
RR of all-cause mortality (OPT)	1.563	1.163	9,109	0.07	124,733
		2.083	12,972	0.58	22,240
Univariate sensitivity analysis results for OPT vs. ICD + OPT					
Base case	-	-	287	0.10	2,824
Device lifetime (CRT-D)	(~7y)	(~13y)	-6,129	0.12	Dominant
		(~4y)	8,653	0.07	123,385

Device lifetime (ICD)	(~ 8 years)	(~13 years)	3,505	0.10	35,868
		- (~5 years)	-5,086	0.11	Dominant
Baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D)	0.0285	0.0146	-4,565	-0.09	49,987
		0.0424	2,086	0.19	10,896
RR of hospitalisation for non-fatal arrhythmia (OPT)	1	0.8	-1,978	0.04	Dominant
		1.2	1,923	0.15	13,107
RR of hospitalisation for non-fatal arrhythmia (ICD)	1.11	0.88	2,330	0.10	22,346
		1.41	-2,334	0.10	Dominant
Baseline risk of all-cause mortality (CRT-D), ln(λ),γ	-6.334, 1.234	-6.467, 1.198	2,047	0.14	14,124
		-6.202, 1.270	-1,092	0.06	Dominant
Lead displacement CRT-D	0.0037	0.0004	-1,083	0.11	Dominant
		0.0071	1,600	0.09	17,916

Table 10: Population 3 scenario analysis

Scenario analyses	
Shorter devices' lifetime (using the device lifetime estimates in Fox and colleagues	OPT dominated ICD + OPT, CRT-D + OPT extendedly dominated CRT-P + OPT ICER for CRT-D + OPT vs. ICD + OPT: £23,690 per QALY gained
Estimates of all-cause mortality reported for men in the CRT-D arm, and the respective hazard	Both CRT-P+OPT and CRT-D+OPT extendedly dominated by ICD+OPT ICER for ICD+OPT vs. OPT: £154 per QALY gained

ratio for ICD for the whole population, from the MADIT-CRT trial (1.00, 95% CI 0.69, 1.44).			
Alternative assumption about device related cost	Upper limit of 95% CI	CRT-D + OPT vs. ICD + OPT	£50,824
		CRT-D + OPT vs.CRT-P + OPT	£43,853
		CRT-D + OPT vs.OPT alone	£60,864
	lower limit of 95% CI	CRT-D + OPT vs.ICD + OPT	£22,271
		CRT-D + OPT vs.CRT-P + OPT	£13,829
		CRT-D + OPT vs.OPT alone	£28,200