

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

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

1 Guidance

1.1 Implantable cardioverter defibrillators (ICDs) are recommended as options for:

- treating people with previous serious ventricular arrhythmia, that is, for people who, without a treatable cause:
 - have survived a cardiac arrest caused by either ventricular tachycardia (VT) or ventricular fibrillation **or**
 - have spontaneous sustained VT causing syncope or significant haemodynamic compromise **or**
 - have sustained VT without syncope or cardiac arrest, and also have an associated reduction in left ventricular ejection fraction (LVEF) of less than 35% but their symptoms are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.
- treating people who:
 - have a familial cardiac condition with a high risk of sudden death, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia **or**
 - have undergone surgical repair of congenital heart disease.

1.2 Implantable cardioverter defibrillators, cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with an LVEF of 35% or less as specified in table 1.

Table 1 Treatment options with ICD or CRT for people with heart failure who have left ventricular dysfunction with an LVEF of 35% (according to NYHA class, QRS duration and presence of LBBB)

QRS interval	NYHA class			
	I	II	III	IV
<120 milliseconds	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P
LBBB, left bundle branch block				

2 Clinical need and practice

Arrhythmia

2.1 Arrhythmia is a condition where the heart contracts irregularly, or at a faster or slower pace than normal. It is caused by an abnormality in the myocardial tissue, or in the electrical conduction system of the heart. Arrhythmias that arise from ventricles (ventricular arrhythmias) can occur unexpectedly and can cause sudden death when insufficient blood is pumped out by the heart to sustain life.

Ventricular arrhythmias include ventricular tachycardia and ventricular fibrillation. In ventricular tachycardia, the ventricles beat faster than normal (at between 120 and 200 beats per minute). In ventricular fibrillation, electrical impulses rapidly start firing from multiple sites in the ventricles, resulting in an uncoordinated, irregular rhythm.

- 2.2 Ventricular arrhythmias most commonly occur in people with underlying heart disease. Approximately 75–80% of the 70,000 sudden cardiac deaths in England and Wales in 2010 could be attributed to ventricular arrhythmias. The average chance of survival of adults after an out-of-hospital episode of ventricular arrhythmia has been reported to be as low as 7%. However, with appropriate treatment, recent studies have reported 5-year survival of 69–100% in people who had survived a cardiac arrest.
- 2.3 Many patients presenting with arrhythmias, with or without symptoms, are treated with antiarrhythmic drug therapy. However, antiarrhythmic drugs may not be optimally effective and need careful and frequent adjustment. This can be confusing for patients and may lead to missed doses, taking the wrong dose or overdose. Many antiarrhythmic drugs result in tiredness, inability to perform day-to-day activities and dependence on carers, and consequently increase the risk of depression. Antiarrhythmic drugs also have many side effects on a range of organs including the thyroid, liver and lungs.
- 2.4 Chronic prophylactic antiarrhythmic drug therapy aims to suppress the development of arrhythmias, but does not stop an arrhythmia once it has started. People who survive a first episode of life-threatening ventricular arrhythmia are at high risk of further episodes. For preventing further life-threatening events in survivors of previous serious ventricular arrhythmias, people are usually treated with implantable cardioverter defibrillators (ICDs).

Preventing sudden cardiac death in someone who has never had a cardiac arrest or ventricular arrhythmia is challenging because it requires identifying a person with substantial level of risk. Many risk factors for sudden cardiac death have been reported such as age, hereditary factors, having a high risk for coronary artery disease, inflammatory markers, hypertension, left ventricular hypertrophy, conduction abnormalities (for example, left bundle branch block), obesity, diabetes and lifestyle factors. There is currently no optimal strategy for risk stratification.

Heart failure

2.5 Heart failure is caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently as a pump to support circulation. It causes breathlessness, fatigue and fluid retention. Clinically it is classified using the New York Heart Association (NYHA) functional class system, ranging from class I (no limitation of physical activity or symptoms, but heart failure symptoms in the past) 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, 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 left ventricular ejection fraction. The scope for this appraisal focuses on left and biventricular heart failure.

2.6 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 left ventricular systolic dysfunction. 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; this is the most common cause of death in people with mild to moderate heart failure.

- 2.7 Treatment of heart failure aims to improve life expectancy and quality of life. [Chronic heart failure: management of chronic heart failure in adults in primary and secondary care](#) (NICE clinical guideline 108) recommends pharmacological treatment initially. However, as the condition becomes more severe, cardiac function and symptoms may no longer be controlled by pharmacological treatment alone, and can be improved by the implantation of a cardiac rhythm device which can sense and stimulate the atria and right and left ventricles independently. These devices are known as cardiac resynchronisation therapy pacing (CRT-P) devices or cardiac resynchronisation therapy defibrillator (CRT-D) devices.

3 The technologies

- 3.1 Implantable cardioverter defibrillators (ICDs) are small, battery-powered devices that are implanted under the skin just below the collarbone, with leads (tiny wires) inserted 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 rhythm if necessary. Based on average selling prices aggregated across all manufacturers of ICDs sold in the UK to the NHS in the financial year of 2011, the cost of a complete ICD system was estimated at £9692.
- 3.2 Cardiac resynchronisation therapy with pacing (CRT-P), also known as biventricular pacing, involves implanting a pulse generator in the upper chest. Three leads connect this to the right atrium and both ventricles, and the device resynchronises the contraction of the ventricles, thereby improving the heart's pumping

efficiency. Based on average selling prices aggregated from devices sold in the UK to the NHS across all manufacturers in the financial year of 2011, the cost of a complete CRT-P system is estimated to be £3411.

- 3.3 Cardiac resynchronisation therapy with a defibrillator device (CRT-D) combines CRT-P and ICD devices. A CRT-D device defibrillates the heart internally in the event of an acute arrhythmic event and improves ventricular efficiency and blood flow. Based on average selling prices aggregated from devices sold in the UK to the NHS across all manufacturers in the financial year of 2011, the cost of a complete CRT-D system is estimated to be £12,293.
- 3.4 Costs may vary in different settings because of negotiated procurement discounts.
- 3.5 Adverse events from implantable devices are mostly related to implantation-related complications and include coronary vein dissection, coronary vein perforation, lead dislodgement, infection and death. Patients with defibrillator devices (ICD and CRT-D) who experience defibrillator shocks may have adverse psychological symptoms (notably anxiety).

4 Evidence and interpretation

The Appraisal Committee (section 9) considered evidence from a number of sources (section 10).

4.1 Clinical effectiveness

- 4.1.1 The Assessment Group and the manufacturers' submission took different approaches to this appraisal. The Assessment Group used study-level data, and its analyses addressed whether the devices are effective in the populations defined in the scope (described in sections 4.1.4–4.1.35). The manufacturers' submission used

individual patient-level data from trials and its analyses addressed the subgroups in which the devices were most effective (described in sections 4.1.36–4.1.40).

4.1.2 The Assessment Group's systematic review identified 26 relevant randomised controlled trials covering the population groups defined in the scope. Although there was overlap between the trials included in the assessment report and the joint industry manufacturers' submission, the RESPOND, VECTOR and REVERSE trials were included only in the manufacturers' submission and the DINAMIT, IRIS and CABG Patch trials were included only in the assessment report. In addition, the 4 trials addressing the use of implantable cardioverter defibrillators (ICDs) for secondary prevention were not considered in the manufacturers' submission.

4.1.3 The Association of British Healthcare Industries submitted a joint submission on behalf of the 5 device manufacturers relevant to this appraisal (Biotronik UK, Boston Scientific, Medtronic UK, Sorin Group and St Jude Medical). The manufacturers' submission focused on adults with heart failure (New York Heart Association [NYHA] class I to IV) and a left ventricular ejection fraction (LVEF) of 35% or less, and at risk of sudden cardiac death. No evidence was presented for secondary prevention of sudden cardiac death or for primary prevention in patients with familial cardiac conditions. The manufacturers identified 22 published clinical-effectiveness studies for ICD and for cardiac resynchronisation therapy with pacing (CRT-P) and with a defibrillator (CRT-D) in patients with heart failure and presented an individual patient data network meta-analysis (IPD NMA) based on 13 of these trials, including over 12,638 patients and accounting for around 95% of patients from all 22 studies.

Assessment Group report

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

- 4.1.4 The Assessment Group identified 13 unblinded randomised controlled trials in people at risk of sudden cardiac death as a result of ventricular arrhythmias (population 1) and synthesised the trial results based on the different risk criteria for sudden cardiac deaths used in the trials. Patients in the intervention arm of most trials received medical therapy in addition to the intervention. ICD for secondary prevention was studied in 4 trials: AVID (n=1016), CASH (n=288), CIDS (n=659) and DEBUT (n=66; pilot=20 and main study=46). The average length of follow-up varied from 18 months to 57 months across the trials. LVEF varied from 30% to 70% across the trials. All patients in the DEBUT trial had NYHA class I congestive heart failure and most patients in the remaining trials were in NYHA class I or II.
- 4.1.5 The Assessment Group conducted a meta-analysis that indicated that, compared with medical treatment alone, ICD treatment resulted in reductions in all-cause mortality (relative risk [RR] 0.75, 95% confidence interval [CI] 0.61 to 0.93), total cardiac death (RR 0.74, 95% CI 0.61 to 0.91) and sudden cardiac death (RR 0.49, 95% CI 0.34 to 0.69). The AVID and CIDS trials assessed quality of life through separate sub studies using a range of generic and condition-specific measures. The AVID trial reported that there were no statistically significant differences in SF-36 scores between groups at 12-month follow-up. ICD shocks were reported to have a negative impact on quality-of-life scores for ICDs across the different measures. The most frequently reported adverse events with ICDs included defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia (19%, DEBUT); T-wave oversensing (8%, DEBUT); device-related discomfort

(7.6%, CIDS); ICDs permanently or temporarily explanted because of infection, heart transplantation or patient preference (5%, CIDS); 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).

- 4.1.6 The DINAMIT (n=674) and IRIS (n=898) trials compared ICDs with medical therapy alone in people with a recent myocardial infarction. 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 remainder 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. A meta-analysis of the 2 trials conducted by the Assessment Group reported no difference in all-cause mortality (RR 1.04, 95% CI 0.86 to 1.25), total cardiac deaths (RR 0.97, 95% CI 0.79 to 1.20) or non-cardiac deaths (RR 1.39, 95% CI 0.86 to 2.27) with ICDs compared with medical therapy. However, people with ICDs had a lower risk of sudden cardiac death (RR 0.45, 95% CI 0.31 to 0.64), but a higher risk of non-arrhythmic cardiac death (RR 1.77, 95% CI 1.30 to 2.40; $p=0.0002$) than people receiving medical therapy. The IRIS trial found no statistically significant difference between groups for cumulative mortality. In the IRIS trial, 15.7% of patients in the ICD group experienced clinically significant complications and 1.7% of patients died within 30 days of implantation surgery. In the DINAMIT trial, 8.1% of patients experienced device-related complications, but no related deaths were reported.
- 4.1.7 The MADIT I (n=196) and MADIT II (n=1232) trials compared ICDs with medical therapy in people who had had myocardial infarction

at least 3 weeks or 1 month before trial entry respectively. The average length of follow-up was 27 months for MADIT I 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 I and 23% in MADIT II. Both the MADIT I and MADIT II trials reported a reduction in all-cause mortality with ICDs compared with medical therapy alone, reporting hazard ratios of 0.46 (95% CI 0.26 to 0.82) and 0.69 (95% CI 0.51 to 0.93) respectively and these results were supported by a meta-analysis conducted by the Assessment Group (RR 0.57, 95% CI 0.33 to 0.97). The meta-analysis also supported the findings from the trials with regard to secondary outcomes reporting a relative risk of 0.59 (95% CI 0.42 to 0.83) for total cardiac deaths, and a relative risk of 0.36 (95% CI 0.23 to 0.55) for sudden cardiac death for ICDs compared with medical therapy. No differences between groups were found in the trials for non-arrhythmic cardiac deaths or for non-cardiac deaths. The MADIT I trial reported a similar hospitalisation rate for the groups per 1000 months follow-up (ICDs 11.3 months, medical therapy 9.4 months). It also reported that the proportion of hospitalisations due to heart failure was higher in the ICD group (ICDs 19.9%, medical therapy 14.9%). The MADIT II trial assessed quality of life using 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).

- 4.1.8 The AMIOVIRT (n=103), CAT (n=104) and DEFINITE (n=458) trials compared ICDs with medical therapy alone in people with non-ischaemic or idiopathic dilated cardiomyopathy (primary prevention). The medical therapy in the CAT trial was not

considered optimal by current standards because of low beta-blocker use. None of the trials reported a statistically significant difference in all-cause mortality with ICDs compared with medical therapy alone. These results were supported by a meta-analysis by the Assessment Group that 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). A meta-analysis of the AMIOVIRT and DEFINITE trials found a statistically significant reduction in sudden cardiac death with ICDs, with a risk ratio of 0.26 (95% CI 0.09 to 0.77).

4.1.9 The CABG Patch trial (n=900) compared ICDs 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 was not optimal by current standards, and the excessive use of antiarrhythmic drugs in the ICD arm may have offset some of the benefits from ICDs. The mean follow-up was 32 months and mean LVEF was 27%. Most patients were in NYHA class II or III. The results showed no difference in all-cause mortality, total cardiac deaths, non-arrhythmic cardiac death, non-cardiac death and sudden cardiac death for the ICD group compared with medical therapy. 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-month follow-up. 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 and mental health, satisfaction with appearance and satisfaction with scar.

4.1.10 SCD-HeFT (n=2521) was a 3-arm trial that evaluated ICDs in a broad population of patients with mild to moderate heart failure.

Mean follow-up was 46 months and mean LVEF was 25%. Over 70% of patients were in NYHA class II, with the remainder in NYHA class III. The primary outcome of all-cause mortality was lower in the ICD group than in the combined placebo and medical therapy group (hazard ratio [HR] 0.77, 97.5% CI 0.62 to 0.96). Lower rates of total cardiac death (HR 0.76, 95% CI 0.60 to 0.95) and sudden cardiac death (risk ratio 0.44, 95% CI 0.31 to 0.61) were also found for ICDs than in the combined placebo and medical therapy groups.

- 4.1.11 The SCD-HeFT trial reported health-related quality-of-life scores at baseline and 3, 12 and 30 months follow-up using the Duke Activity Status Index, Mental Health Inventory 5, Minnesota Living with Heart Failure questionnaire (MLHFQ) and the global health status. The only statistically significant differences between ICDs and placebo were in median Mental Health Inventory 5 scores and global health status at 3 and 12 months (but these differences were not maintained at 30 months); and in MLHFQ score at 3 months (but this benefit was not maintained at 12 months). A statistically significant decrease in perception 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.
- 4.1.12 The 9 randomised controlled trials evaluating ICDs for primary prevention reported adverse event rates of 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 between 12% and 55% in the 3 trials reporting them. Lead, electrode or defibrillator generator-related problems affected 1.8% (MADIT II) to 14% (CAT) of people in the 5 trials that reported them.

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

4.1.13 The Assessment Group identified 4 multicentre randomised controlled trials comparing CRT-P with medical therapy in people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony (population 2). 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 because all patients had a CRT-P device implanted, but investigators inactivated the device in the control group. The MUSTIC trial used a randomised crossover design, with 3 months follow-up for each of the 2 crossover periods and the Assessment Group stated that the crossover design was appropriate. All trials included people with NYHA class III or IV heart failure, with most patients in NYHA class III and with LVEF less than 35%. Average LVEF was about 22% in MIRACLE and COMPANION, and 25% in CARE-HF. The QRS duration was prolonged (more than 150 milliseconds) across all 4 trials. An intention-to-treat analysis was performed in the trials.

CRT-P compared with medical therapy

4.1.14 For CRT-P compared with medical therapy, the CARE-HF trial reported a reduction in all-cause mortality after a mean follow-up of 37.4 months (HR 0.60, 95% CI 0.47 to 0.77). 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). Differences in all-cause mortality observed in the other 3 trials were not statistically significant. A meta-analysis of all 4 trials conducted by the Assessment Group found that CRT-P statistically significantly reduced all-cause mortality compared with medical therapy with a risk ratio of 0.75 (95% CI 0.58 to 0.96).

- 4.1.15 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. In the CARE-HF trial, fewer patients in the CRT-P group experienced sudden cardiac death than in the medical therapy group 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 that 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).
- 4.1.16 In the CARE-HF trial, fewer patients in the CRT-P group died from heart failure compared with the medical therapy group 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 decreased death due to heart failure (RR 0.67, 95% CI 0.51 to 0.88).
- 4.1.17 All 4 trials measured hospitalisations because of heart failure and all except MUSTIC reported lower rates with CRT-P than 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). The Assessment Group calculated the rate of hospitalisation due to heart failure for each trial and combined these in a meta-analysis. This demonstrated a statistically significant reduction in the rate of heart failure hospitalisations with CRT-P compared with medical therapy (RR 0.58, 95% CI 0.35 to 0.96). Three trials (CARE-HF, MIRACLE and MUSTIC) reported a benefit with CRT-P with regard to '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) than with medical therapy. Three trials (CARE-HF, COMPANION and MIRACLE) also reported a greater proportion of patients with improvement in NYHA class with CRT-P than with medical therapy. The Assessment Group conducted a meta-analysis that showed an increase in the proportion of people with an improvement in NYHA status by 1 or more class with CRT-P compared with medical therapy (RR 1.68, 95% CI 1.52 to 1.86).

4.1.18 The CARE-HF trial reported that the risk of arrhythmias was higher with CRT-P than with medical therapy with a risk ratio of 1.54 (95% CI 1.07 to 2.23). The CARE-HF, COMPANION and MIRACLE trials reported a statistically significantly 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 with respect to improvement in 1 or more NYHA class estimated a risk ratio of 1.68 (95% CI 1.52 to 1.86). The MIRACLE trial measured change in LVEF and reported an improvement with CRT-P at 6 months (increase of 4.6%), compared with a decline (reduction of 0.2%) with medical therapy.

4.1.19 The COMPANION, MIRACLE and MUSTIC trials reported that CRT-P improved exercise capacity more than medical therapy, as measured by the distance walked in 6 minutes. A meta-analysis of these trials showed a statistically significant improvement with CRT-P compared with medical therapy (mean difference 38.14 metres [95% CI 21.74 to 54.54, $p < 0.00001$]).

4.1.20 All trials found that CRT-P improved MLHFQ 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).

CARE-HF also reported improvements in EQ-5D scores, 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 gained was higher with CRT-P at 18 months (CRT-P 0.95 compared with medical therapy 0.82, $p<0.0001$).

CRT-D compared with medical therapy

4.1.21 Data from the COMPANION trial were available for a comparison of CRT-D with medical therapy. Results from this trial reported reductions with CRT-D compared with medical therapy for the outcomes of all-cause mortality (HR 0.64, 95% CI 0.48 to 0.86), total cardiac deaths (RR 0.68, 95% CI 0.50 to 0.93), sudden cardiac deaths (HR 0.44, 95% CI 0.23 to 0.86) and heart failure hospitalisations (RR 0.77, 95% CI 0.63 to 0.93). There were no differences between CRT-D and medical therapy for the outcomes of heart failure deaths (HR 0.73, 95% CI 0.47 to 1.11) and non-cardiac deaths (CRT-D 2.3% compared with medical therapy 3.6%). The proportions of people with improvements in 1 or more NYHA class (57% compared with 38%, $p<0.001$), in exercise capacity (change in 6-minute walking distance; 46 metres compared with 1 metre, $p<0.001$), and in health-related quality-of-life scores at 6 months measured by MLHFQ score (-26 compared with -12 , $p<0.001$) were statistically significantly greater with CRT-D than with medical therapy.

CRT-P compared with CRT-D

4.1.22 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 to compare CRT-P with CRT-D and therefore all results for this comparison should be interpreted with caution. The results indicated that rates of total cardiac deaths and sudden cardiac deaths were higher with CRT-P than with CRT-D,

with risk ratios of 1.38 (95% CI 1.06 to 1.81) and 2.72 (95% CI 1.58 to 4.68) respectively.

- 4.1.23 The Assessment Group stated that reporting of adverse events was limited in all 4 trials. The rate of unsuccessful implantation ranged between 4.6% (CARE-HF) and 12.6% (COMPANION). Device-related deaths reported in the trials varied between 0.2% (CARE-HF) and 0.8% (COMPANION) for those with CRT-P and 0.5% for those with CRT-D (COMPANION). In the COMPANION trial, the rate of moderate or severe adverse events related to the implantation procedure was 10% with CRT-P and 8% with CRT-D, with 13% and 9% of CRT-P and CRT-D implantations being unsuccessful. Reported complications included lead displacements, infections and coronary sinus dissections.

People with heart failure because of left ventricular systolic dysfunction and cardiac dyssynchrony who are also at risk of sudden cardiac death because of ventricular arrhythmias (population 3)

- 4.1.24 The Assessment Group identified 9 trials comparing CRT-D with ICDs in people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony who are also at risk of sudden cardiac death due to ventricular arrhythmia (population 3). 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 had a CRT-D device implanted, 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. Patients also received medical therapy (except in the Piccirillo trial). No trials comparing CRT-D with medical therapy or with CRT-P were identified for this population.

- 4.1.25 The RethinQ and RHYTHM ICD trials were described as double-blind but the Assessment Group stated that details were not reported. 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 trial group assignments.
- 4.1.26 Most patients in MADIT-CRT, MIRACLE ICD II and RAFT were in NYHA class II, whereas in CONTAK-CD, MIRACLE ICD, RethinQ and RHYTHM ICD most patients were in NYHA class III. NYHA class was not reported by Pinter, although the eligibility criteria specified mild to moderate heart failure. Most patients in Piccirillo were in NYHA class I. Average length of follow-up ranged between 6 and 40 months across the trials. Prolonged QRS duration on electrocardiogram (ECG) of 120 milliseconds or more to 150 milliseconds or more in different trials was used to define cardiac dyssynchrony in all trials except RethinQ in which people with a short QRS interval (less than 130 milliseconds) were included on the basis of mechanical dyssynchrony apparent on echocardiography. Mean LVEF ranged from 21% (CONTAK-CD) to 26% (RethinQ). Crossover between groups was reported in all trials. 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 being 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.
- 4.1.27 The Assessment Group stated that only 4 trials were adequately powered to show a difference in their primary outcomes. These 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 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.

- 4.1.28 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), whereas 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 occurred in either group. The Assessment Group also conducted a meta-analysis pooling data from the trials, which found that CRT-D reduced the risk of all-cause mortality significantly compared with ICDs with a risk ratio of 0.84 (95% CI 0.73 to 0.96). The Assessment Group commented that the results were strongly influenced by the RAFT trial and when this trial was removed from the analysis the differences were no longer statistically significant.
- 4.1.29 All but the MADIT-CRT and Piccirillo trials reported data on total cardiac deaths, although only the RAFT trial compared results between groups statistically. 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) in favour of CRT-D compared with ICDs. The results were no longer significant if the RAFT trial was excluded from the meta-analysis. Rates of death due to heart failure or sudden cardiac death were not statistically significantly

different across the CRT-D and ICD groups in any of the trials reporting these, and this was also the case 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 were 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 trial indicated that the probability of event-free survival at 5 years was 57.6% with CRT-D and 48.7% with ICDs.

4.1.30 The RAFT trial found a 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). The CONTAK-CD and Piccirillo trials found no statistically 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 ICDs with a risk ratio of 0.75 (95% CI 0.64 to 0.88, $p=0.0005$). The CONTAK-CD, MIRACLE ICD, MIRACLE ICD II and Pinter trials reported the number of patients experiencing at least 1 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 1 arrhythmia with a risk ratio of 0.90 (95% CI 0.71 to 1.14, $p=0.38$).

4.1.31 The MIRACLE ICD, MIRACLE ICD II and RHYTHM ICD trials reported an improvement in mean or median NYHA class among people with CRT-D compared with people with ICDs. Combining these studies in a 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 Piccirillo trials reported the proportion of people who improved by 1 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 the 2 groups, with a risk ratio of 1.81 (95% CI 0.91 to 3.60).

- 4.1.32 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 ICDs, whereas 3 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 meta-analysis indicated a statistically significant improvement in LVEF with CRT-D compared with ICDs with a mean difference in mean LVEF of 2.15 (95% CI 0.45 to 3.86, $p=0.01$).
- 4.1.33 All except the RAFT and Piccirillo trials reported change in exercise capacity measured by distance walked in 6 minutes, exercise duration, peak VO_2 (peak oxygen uptake), and proportion of patients 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 VO_2 , 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 indicating a

mean difference of 14.5 metres between groups (95% CI 2.9 to 26.1, $p=0.01$).

- 4.1.34 All except the RAFT and Piccirillo trials reported changes in quality of life at 6 months using the MLHFQ. Meta-analysis of these trials indicated a statistically significant improvement in quality of life with CRT-D compared with ICDs, with a mean difference of -6.9 in MLHFQ 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 with 6-month changes.
- 4.1.35 The Assessment Group stated that reporting of adverse events was inconsistent across the trials. The RAFT trial compared adverse events between groups statistically and found that rates of device- or implantation-related complications within 30 days of implantation were significantly higher in the CRT-D group than in the ICD group (13.3% compared with 6.8%, $p<0.001$); this also applied to 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 ICDs.

Manufacturers' submission

- 4.1.36 The manufacturers presented an individual patient data network meta-analysis (IPD NMA) using meta-regression to assess the effectiveness of ICDs, CRT-P and CRT-D in different subgroups of people with heart failure. The manufacturers stated that given the heterogeneous patient population, an IPD NMA would allow the differences in baseline risk and relative treatment effects of the devices to be better captured. Although the outcome data for longer

follow-up periods were available, only data up to the original trial protocol-specified 'data-lock' follow-up period were included in the analysis. The median data-lock period in the included trials ranged from 3 to 41 months, whereas the longest individual follow-up data in the IPD NMA were recorded at 7.5 years. Data from the data-lock follow-up period were included in the analysis to reduce bias introduced by crossover from a control group to a device when blinding was removed.

- 4.1.37 Data on outcomes relevant to the economic analysis, that is, all-cause mortality, all-cause hospitalisation and health-related quality of life were synthesised from the individual patient data. 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. The IPD NMA adopted a multivariate approach using meta-regression to assess the effects of the different interventions on people with heart failure for the 3 outcomes, taking into account the impact of different patient characteristics (covariables).
- 4.1.38 The manufacturers identified covariables using previous NICE guidance, a review of existing risk scores, a review of treatment effect modifiers in previous trials and clinical opinion. The following covariables were found to be important and were investigated further for the interactions with baseline risk and treatment effects of devices on mortality, hospitalisation and health-related quality of life: age, sex, geographic region (USA compared with non-USA), NYHA class, ischaemic aetiology, LVEF, QRS duration and left bundle branch block (LBBB). The other covariables identified but not included in the analyses were history of myocardial infarction, sinus rhythm, mechanical dyssynchrony, previous pacing, history of previous ventricular tachycardia or ventricular fibrillation, non-sustained ventricular tachycardia on ECG, inducible ventricular tachycardia on electrophysiology testing and diuretic use.

- 4.1.39 For the IPD NMA the manufacturers estimated a baseline rate for each outcome, independent of the treatment effects of the devices, from pooled data of all patients randomised to medical therapy in the trials reporting the specific outcome irrespective of the device assessed. Device-specific treatment effects were then estimated using all available data from the trials. In both stages of the analysis, patient characteristics were included as covariables to incorporate baseline risk and treatment effect modifiers.
- 4.1.40 The manufacturers' IPD NMA found CRT-D to have the greatest effect on all-cause mortality. Age, sex, QRS duration and LBBB status were found to independently predict the magnitude of benefit associated with the devices. For all-cause hospitalisation, therapy with all devices reduced admission rates across all NYHA classes. For health-related quality of life, baseline estimates using EQ-5D from the individual patient data showed that patients in NYHA classes I and II had similar values to the population norms, whereas patients in NYHA classes III and IV had values that were progressively lower. Limited EQ-5D data were available for all devices in patients in NYHA class IV, and defibrillator devices (ICD and CRT-D) in patients in NYHA class III. The analyses showed that CRT-D had an adverse impact on health-related quality of life of patients with NYHA class III and IV symptoms. This was in contrast to CRT-P, which statistically significantly improved health-related quality of life in these patients. The manufacturers stated that this result was counterintuitive and therefore assumed that CRT-D had the same effect on health-related quality of life as CRT-P for patients in NYHA classes III and IV, and ICDs had an effect on health-related quality of life in patients in NYHA classes I and II only. The results from the IPD NMA are academic in confidence, and therefore cannot be presented here.

4.2 **Cost effectiveness**

4.2.1 The differences in approach taken to this appraisal by the Assessment Group and the manufacturers and the different data sources available to them (described in sections 4.1.1 to 4.1.3) were carried through to the economic analyses. The Assessment Group presented cost-effectiveness results for each of the 3 populations outlined in the scope, whereas the manufacturers modelled the individual patient data for 12,638 patients, splitting them into subgroups according to NYHA class, QRS duration, LBBB status and aetiology of heart disease, and reporting cost-effectiveness results for each subgroup. The sections below briefly summarise the Assessment Group's model and results, the manufacturers' approach and the Assessment Group's critique of these analyses.

Assessment Group's model and results

4.2.2 The Assessment Group adapted the model developed by Fox et al. for [Cardiac resynchronisation therapy for the treatment of heart failure](#) (NICE technology appraisal guidance 120). This was a Markov model with monthly cycles over a lifetime time horizon and all future costs and benefits discounted at a rate of 3.5%. Population 1, that is, people at risk of sudden cardiac death as a result of ventricular arrhythmias, had not been included in the previous model and the Assessment Group adapted the pathways for this population based on reviews of other models and expert opinion. The Assessment Group model compared the strategies (devices or optimal pharmacological therapy [OPT]) as outlined in the scope. For population 1, ICD plus OPT was compared with OPT alone. For population 2, CRT-P plus OPT and CRT-D plus OPT were compared with each other and with OPT alone in a series of pairwise analyses. For population 3, the Assessment

Group reported an incremental analysis comparing OPT, ICD plus OPT, CRT-P plus OPT and CRT-D plus OPT.

- 4.2.3 The treatment pathways in the model allowed crossover, that is, patients initially treated with OPT could subsequently receive devices when considered clinically necessary, for example if they were hospitalised for heart failure or for major arrhythmia. The model also allowed for upgrade of devices, that is, patients initially treated with a device could subsequently change devices if considered clinically necessary.
- 4.2.4 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 receiving devices, device-specific hazard ratios or relative risks from the Assessment Group’s meta-analyses were applied to baseline mortality. Data for the model parameters were sourced mainly from the trials but also from the literature.
- 4.2.5 The utility values for people in stable health states were 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 model assumed similar utility values for patients with CRT, ICDs or OPT alone for the same NYHA class. To estimate resource use, the Assessment Group considered costs of devices, device implantation, device-related complications and maintenance, costs of hospitalisation because of heart failure or severe arrhythmia, and costs of medication and heart transplantation.

4.2.6 The Assessment Group's economic model indicated that initial treatment of patients at increased risk of sudden cardiac death (population 1) with ICDs in combination with OPT had an ICER of £19,479 per QALY gained compared with initial treatment with OPT alone. The ICERs in other groups analysed (that is, people with remote myocardial infarction, a broad population with mild to moderate heart failure, and patients with non-ischaemic cardiomyopathy) ranged between £14,231 and £29,756 per QALY gained. For patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony (population 2), the base-case analysis suggested the addition of either CRT-P or CRT-D to OPT in the initial stage of management of heart failure could be considered cost effective if the maximum acceptable ICER was £30,000 per QALY gained and that CRT-D plus OPT when compared with CRT-P plus OPT was also likely to be cost effective if the maximum acceptable ICER was £30,000 per QALY gained. For people with both conditions (population 3), the Assessment Group's base-case analysis found that if the maximum acceptable ICER was £30,000 per QALY gained, initial management with any implantable device (ICD, CRT-P or CRT-D) was not a cost-effective strategy.

Manufacturers' submission

4.2.7 The manufacturers' submission included a survival-based model to estimate the relative cost effectiveness of OPT, ICDs, CRT-P and CRT-D, compared with each other in a fully incremental analysis. The UK NHS and personal social services perspective was adopted and the model included monthly cycles and a lifetime time horizon. Costs and health benefits were discounted at 3.5%. The model had 2 health states: alive and dead. The manufacturers stated that death is the main clinical event for the patient population considered in this appraisal and that by modelling mortality directly via a series of covariate-based regression equations (for baseline

risk and treatment effect), the long-term data available could be used to carry out the analysis taking into account 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 of capturing the effect on health-related quality of life using time-dependent progression through NYHA classes was technically difficult and less accurate.

4.2.8 Individual patient data from 12,638 adults were used to inform the manufacturers' model. All had heart failure with an LVEF of 35% or less, and/or were at risk of sudden cardiac death. The results for this heterogeneous group of patients were generated in a 2-stage process. In the first stage, estimates of costs incurred and QALYs gained were derived for all relevant devices from 4992 patient profiles based on 4 LVEF categories, 4 NYHA classes of heart failure, 2 aetiologies of heart disease (ischaemic or non-ischaemic), 3 QRS categories, 2 LBBB categories, 2 sex groups and 13 age categories. In the second stage, results were aggregated over LVEF, age and sex categories and presented for 48 subgroups according to NYHA class, QRS duration, LBBB status and aetiology of heart disease (ischaemic or non-ischaemic). In the revised analysis, based on a request by the Committee, the manufacturers combined the ischaemic and non-ischaemic disease patient groups together, therefore presenting cost-effectiveness results for 24 subgroups rather than 48 as in the original submission.

4.2.9 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 baseline probability of all-cause hospitalisation was estimated as the number

of events per month from patients randomised to medical therapy using individual patient data from 11 clinical trials. The relative effectiveness of devices was estimated from the IPD NMA. In the base case, the manufacturers assumed a constant duration of effect of 7.5 years for all-cause mortality, followed by tapering (a gradual linear decrease) up to 20 years. The assumption that 7.5 years is the duration of constant effect was based on the longest individual follow-up duration included in the IPD NMA.

- 4.2.10 The manufacturers justified this assumption of a constant treatment effect for 7.5 years on the basis that there was no evidence that the proportional hazards assumption in the Cox regression analysis was violated and that long-term follow-up in some trials showed maintenance of benefit beyond the data-lock period. Long-term data from the CARE-HF trial showed that the hazard ratio for all-cause mortality at a mean follow-up of 56 months in the CRT-P arm and 50 months in the OPT arm was 0.77 (95% CI 0.63 to 0.93) compared with a hazard ratio of 0.64 (95% CI 0.48 to 0.85) at a mean follow-up of 29.4 months (data-lock period), despite 39% of patients in the OPT arms crossing over to receive a CRT device. Similarly, long-term data from the MADIT II trial reported the hazard ratio for all-cause mortality as 0.77 (0.65, 0.91) at a median follow-up of 7.6 years compared with a hazard ratio of 0.69 (0.51, 0.93) at average follow-up of 20 months, despite 34% of control patients crossing over to a device during follow-up.
- 4.2.11 The manufacturers' model introduced a conservative assumption that the benefit would taper linearly following the period of assumed constant benefit such that the hazard ratio would reach 1.0 at 20 years. However, the manufacturers also presented sensitivity analyses assuming lifelong constant treatment effects without any tapering as a more optimistic scenario, and assuming a constant duration of effect for 5 years followed by linear tapering up to

year 20 as a more conservative scenario. The manufacturers also provided a sensitivity analysis assuming a constant duration of effect up to the average duration of trial-specific data-lock durations (2.54 years), followed by linear tapering thereafter up to 20 years.

- 4.2.12 UK device longevity estimates were derived from NHS data from the Central Cardiac Audit Database on all implants from 2000 to 2011 (around 40,000 implants). Device-specific median survival estimates were obtained by fitting Weibull curves to these data. Median time to device failure in the model was 7.1 years for ICDs, 10.4 years for CRT-P and 5.8 years for CRT-D.
- 4.2.13 The manufacturers' model did not include short-term device-related adverse events because the costing approach used to derive total implant costs covered additional costs such as short-term adverse events. Infection following device implantation 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 this was applied to all devices in the first cycle following battery replacement.
- 4.2.14 Resource use included device-related costs, medication costs and costs related to disease progression. Individual patient data from the trials were 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 estimated to be £2295 and the non-heart failure hospitalisation cost was estimated to be £2448. 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. Implantation costs were taken from the Healthcare Resource Group tariff values. Device costs, including implantation costs, were

estimated to be £15,248, £8281 and £17,849 for ICD, CRT-P and CRT-D devices respectively.

4.2.15 The manufacturers' approach assumed that the medical therapy received before and during device treatment would be regarded as optimal by current standards. It also assumed that the drug costs in any given month were based on baseline NYHA class. The proportions of patients using different combinations of a range of drugs, according to their NYHA class, were 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 medical therapy per 1-month cycle was £14.28 for NYHA class I patients and between £22.13 and £22.30 for patients in NYHA classes II to IV.

4.2.16 For modelling health-related quality of life, general UK population utilities were used at baseline and 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 an intervention-specific increment, calculated as the difference between baseline and the first follow-up period. These estimates were derived from published sources and IPD 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 an intervention observed at 6 months would be maintained for 5 years and thereafter would decrease in a linear manner. The model assumed that at 10 years a CRT or ICD device will have no additional benefit over OPT.

4.2.17 The manufacturers stated that combining the ischaemic and non-ischaemic groups (as described in section 4.2.8) resulted in more precise results because each subgroup included larger patient

numbers. The base-case deterministic results were presented for 24 subgroups defined by NYHA class, QRS duration and LBBB status, highlighting the most cost-effective treatment strategy if the maximum acceptable ICER was £30,000, £25,000 and £20,000 per QALY gained for each subgroup, as requested by the Committee. The manufacturers highlighted that the ICERs were in some cases close to the threshold values and also predicted that the ICERs would fall because acquisition costs of the medical devices are expected to reduce over time.

The base-case ICERs for the predicted optimal treatment strategies are summarised in table 2. The ICERs at £30,000 per QALY gained are presented only when the higher maximum acceptable ICER changes the optimal strategy.

Table 2 Manufacturers' base case: predicted optimal treatment strategies and ICERs

		Optimal treatment strategy and base-case ICER	
NYHA class	QRS duration (milliseconds)	Maximum acceptable ICER £25,000 per QALY gained	Maximum acceptable ICER £30,000 per QALY gained
Without LBBB			
I	<120	ICD £24,074	ICD
I	120–149	ICD £16,253	ICD
I	≥150	CRT-D £21,759	CRT-D
II	<120	ICD £24,465	ICD
II	120–149	ICD £16,813	ICD
II	≥150	CRT-D £23,738	CRT-D
With LBBB			
I	<120	OPT	OPT
I	120–149	CRT-D £21,672	CRT-D
I	≥150	CRT-D £17,470	CRT-D
II	<120	OPT	OPT
II	120–149	CRT-D £20,704	CRT-D
II	≥150	CRT-D £17,664	CRT-D
Without LBBB			
III	<120	OPT	ICD £27,826
III	120–149	CRT-D £23,349	CRT-D
III	≥150	CRT-P £13,930	CRT-D £25,200
IV	<120	OPT	OPT
IV	120–149	CRT-P £22,578	CRT-P
IV	≥150	CRT-P £17,175	CRT-P
With LBBB			
III	<120	OPT	OPT
III	120–149	CRT-D	CRT-D

		£24,875	
III	≥150	CRT-P £10,494	CRT-D £28,646
IV	<120	OPT	OPT
IV	120–149	CRT-P £18,664	CRT-P
IV	≥150	CRT-P £14,500	CRT-P
<p>CRT-D, cardiac resynchronisation therapy with defibrillation; CRT-P, cardiac resynchronisation therapy with pacing; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LBBB, left bundle branch block; NYHA, New York Heart Association; OPT, optimal pharmacological therapy; QALY, quality-adjusted life year</p>			

4.2.18 The manufacturer explored the impact of alternative assumptions about the duration of constant mortality benefit on the cost effectiveness of the devices (section 4.2.11). The results for the sensitivity analysis assuming constant mortality benefit for 5 years then linear tapering up to 20 years are summarised in table 3. The ICER for CRT-D compared with CRT-P in the subgroup of patients with NYHA class III symptoms with a QRS duration more than 150 milliseconds with LBBB was £30,548 per QALY gained. The ICERs for ICD compared with OPT in the subgroup of patients with NYHA class II symptoms with a QRS duration between 120 and 149 milliseconds with LBBB and in the patients with NYHA class III, a QRS duration of 120 and 149 milliseconds without LBBB were not available in the manufacturers' sensitivity analyses. Using the manufacturers' additional analyses, the Assessment Group estimated the ICERs in these 2 subgroups to be £23,144 and £24,514 per QALY gained respectively. The ICERs for ICD compared with OPT in the subgroup of patients with NYHA class I symptoms with a QRS duration between 120 and 149 milliseconds with LBBB was available in the manufacturers' analyses and was £21,985 per QALY gained.

Table 3 Manufacturers' sensitivity analyses: predicted optimal treatment strategies and ICERs assuming 5-year duration of constant effect on mortality

		Optimal treatment strategy and ICER	
NYHA class	QRS duration (milliseconds)	Maximum acceptable ICER £25,000 per QALY gained	Maximum acceptable ICER £30,000 per QALY gained
Without LBBB			
I	<120	OPT	ICD £25,714
I	120–149	ICD £16,253	ICD
I	≥150	CRT-D £23,168	CRT-D
II	<120	OPT	ICD £26,181
II	120–149	ICD £16,813	ICD
II	≥150	CRT-D £21,888	ICD £25,267
With LBBB			
I	<120	OPT	OPT
I	120–149	CRT-D £23,080	CRT-D
I	≥150	CRT-D £18,615	CRT-D
II	<120	OPT	OPT
II	120–149	CRT-D £22,049	CRT-D
II	≥150	CRT-D £18,879	CRT-D
Without LBBB			
III	<120	OPT	ICD £29,309
III	120–149	CRT-D £24,311	CRT-D
III	≥150	CRT-P £14,203	CRT-D £26,586
IV	<120	OPT	OPT
IV	120–149	CRT-P £22,702	CRT-P
IV	≥150	CRT-P £17,330	CRT-P
With LBBB			
III	<120	OPT	OPT
III	120–149	CRT-P	CRT-D

		£14,489	£26,192
III	≥150	CRT-P £10,769	CRT-P
IV	<120	OPT	OPT
IV	120–149	CRT-P £18,817	CRT-P
IV	≥150	CRT-P £14,666	CRT-P
<p>CRT-D, cardiac resynchronisation therapy with defibrillation; CRT-P, cardiac resynchronisation therapy with pacing; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LBBB, left bundle branch block; NYHA, New York Heart Association; OPT, optimal pharmacological therapy; QALY, quality-adjusted life year</p>			

4.2.19 In a sensitivity analysis, the manufacturers explored the impact of including costs of counselling for patients receiving defibrillator devices (ICD or CRT-D) on the cost-effectiveness results. Based on clinical advice, the manufacturers assumed that all patients would need 1 consultation session with an arrhythmia nurse and a small proportion of patients (0.5%) would need 1 full psychiatry visit and 4 sessions of cognitive behavioural therapy. The expected per-patient cost of counselling was estimated to be £27.95 and was applied in the first model cycle for patients receiving defibrillator therapy (CRT-D or ICD). The overall impact on the ICERs in all subgroups was negligible with no changes in predicted optimal treatment strategy at the maximum acceptable ICERs of £20,000, £25,000 or £30,000 per QALY gained.

4.2.20 The manufacturers conducted further univariate deterministic sensitivity analyses by varying by 25% non-purchase costs associated with defibrillator devices (ICD or CRT-D) (£5556), all upfront implant costs for patients receiving a CRT-P (£8281), battery replacement costs for defibrillator devices (ICD or CRT-D) (£2748), and the cost of an outpatient visit (£110). Analyses using upper and lower quartile data for hospitalisation costs for heart failure and non-heart failure (£2295 and £2448 respectively) were

also presented. The results indicated that the ICERs were robust to alterations in cost parameters. A full probabilistic sensitivity analysis, exploring uncertainties associated with all parameters simultaneously, was not conducted by the manufacturers. Limited information was presented on the probabilistic sensitivity analyses conducted for 4 different patient profiles, that is: men with and without LBBB, and women with and without LBBB with baseline characteristics of the MADIT-CRT trial (age 65 years, NYHA class II, ischaemic aetiology, QRS >150 milliseconds, LVEF between 20% and 25%). The resulting cost-effectiveness acceptability curves indicated that CRT-D had a similar probability of being cost effective as OPT at a maximum acceptable ICER of £20,000 per QALY gained.

- 4.2.21 The manufacturers also explored the likelihood of crossover or device upgrades in clinical practice. The manufacturers stated that information on device upgrades in UK clinical practice is sparse because the audit conducted by the National Institute for Cardiovascular Outcomes Research did not make a distinction between upgrades and new implants. The manufacturers identified a single-centre, retrospective observational study from the UK that reported an ICD to CRT-D upgrade rate of 3.8% during a mean follow-up period of 48 months (Scott et al. 2012). The manufacturers also cited country-wide data from Sweden that indicated an annual upgrade rate from ICD to CRT (type unspecified) of 0.5%. Clinical opinion from interventional cardiologists also indicated that crossover or device upgrades were rare in clinical practice because of the complexity of the procedure and increased risk of complications. The cardiologists also considered that it was highly unlikely that patients with a CRT-P indication would receive a CRT-D device with the defibrillator function switched off but with the intention to switch it on if the patient developed a life-threatening arrhythmia in the future.

Assessment Group's critique

4.2.22 The Assessment Group critiqued the manufacturers' model and validated the results of the cost-effectiveness analyses. It stated that although 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. For example, ICDs were excluded for NYHA class IV, CRT-P was excluded for NYHA classes I and II and QRS duration of less than 120 milliseconds across all NYHA classes, and CRT-D was excluded for QRS duration of less than 120 milliseconds across all NYHA classes. The Assessment Group stated that these exclusions appeared to be reasonable based on clinical opinion. The Assessment Group stated that the fundamental features of the condition and the impact of the interventions seemed to be captured in the manufacturers' model structure and although no assessment of internal validity of the model was included in the submission, it appeared to be reasonable. 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. The Assessment Group stated that the manufacturers' approach to estimating utility differed from that of most previous models (including Buxton et al. and Fox et al.) in which no benefit from the intervention had been 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 manufacturers' submission. The Assessment Group also 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 for 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 were appropriate and whether the estimates of variation in the probabilistic sensitivity analyses were appropriate to reflect uncertainty in parameter estimates.

4.2.23 The Assessment Group also undertook exploratory sensitivity analyses to determine the main drivers of cost effectiveness in the 3 out of 24 subgroups that consisted of the largest number of patients in the IPD network. These subgroups were patients in NYHA class II with a QRS duration of 150 milliseconds or more with LBBB (subgroup 1), patients in NYHA class III with a QRS duration of 150 milliseconds or more and with LBBB (subgroup 2), and patients in NYHA class II with a QRS duration of less than 120 milliseconds without LBBB (subgroup 3). The results of these analyses showed that for these 3 subgroups the ICERs for the devices were most sensitive to changes to the assumptions regarding the magnitude of treatment effect on mortality and the duration for which the tapering effect was applied.

4.2.24 The Assessment Group commented that the manufacturers' estimation that 0.5% of patients with defibrillators would need additional psychiatry visits and cognitive behavioural therapy sessions was an underestimate but noted that the costs used in the model were based on a more realistic proportion of 5%. The Assessment Group also commented that the per-patient cost of cognitive behavioural therapy was likely to be an underestimate because many patients would need more than 4 sessions and would attend in smaller groups or individual sessions. Based on a conservative assumption of 6 individual sessions per patient, the Assessment Group estimated that the per-patient counselling cost could be as high as £70 compared with the cost of £27.95 used by the manufacturers. The Assessment Group conducted sensitivity

analyses using higher counselling costs for subgroups 1, 2 and 3 and stated that increasing counselling costs had a minimal impact on the ICERs.

- 4.2.25 The Assessment Group's clinical advisers stated that an upgrade from ICD to CRT-D was reasonable and would occur if someone with a pre-existing ICD developed a CRT indication (that is, progressive heart failure and QRS prolongation). The advisers also agreed with the manufacturers that it would be clinically implausible to implant a CRT-D device and not switch the defibrillator on.
- 4.2.26 Following consultation on the appraisal consultation document, the Assessment Group critiqued 3 studies (RethinQ, EchoCRT, Cleland et al. 2013) that were brought to the Committee's attention and consequently factored into the Committee's decision-making (see ACD section 4.3.17).
- 4.2.27 RethinQ (Beshai et al. 2007) was a multicentre, double-blind randomised controlled trial conducted in the USA. It was included in the Assessment Group's systematic review as well as in the manufacturers' IPD NMA. It included 172 patients who had a LVEF of 35% or less, NYHA class III symptoms of heart failure and a QRS duration less than 130 milliseconds, as well as intraventricular mechanical dyssynchrony on echocardiography. All patients had CRT-D implantation and were randomly assigned to have CRT capability turned on (CRT-D group) or off (ICD group). The duration of the study was 6 months and it also reported subgroup analyses based on QRS durations. A statistically significant improvement in the proportion of people with an increase in peak oxygen consumption was found with CRT-D compared with ICD in people with QRS 120–129 milliseconds but not in those with QRS less than 120 milliseconds. CRT-D led to a statistically significantly greater proportion of patients with improvement in NYHA class compared with ICD for both subgroups. The Assessment Group

highlighted that the RethinQ trial was inconclusive overall on mortality, with wide confidence intervals, but the point estimate of effect favoured ICDs. The Assessment Group stated that the RethinQ trial was at low risk of bias but commented that the subgroup analyses lacked statistical power and noted that no tests for interaction were presented and the analyses should be interpreted with caution.

- 4.2.28 EchoCRT (Ruschitzka et al. 2013) was a multicentre, international randomised controlled trial not included in the Assessment Group's systematic review or in the manufacturers' IPD NMA. It included 809 patients with a LVEF of 35% or less; a QRS duration of less than 130 milliseconds; and echocardiographic evidence of left ventricular dyssynchrony. More than 90% of the patients had NYHA class III symptoms of heart failure. All patients had CRT-D implantation and were randomly assigned to have CRT capability turned on (CRT-D group) or off (ICD group). The primary outcome was a composite endpoint of death from any cause or hospitalisation for worsening heart failure. At the mean follow-up of 19.4 months the trial was stopped early because of futility with a potential for harm. EchoCRT explored whether CRT-D had the same effectiveness in subgroups with a QRS duration less than 120 milliseconds and with a QRS duration between 120 and 130 milliseconds for all-cause mortality and the primary composite outcome. There were statistically significantly more deaths in the CRT-D group compared with the ICD group in the subgroup with a QRS duration of less than 120 milliseconds (10.5% compared with 5.2% HR 2.08 [95% CI 1.16 to 3.73]). In contrast, among patients with a QRS duration between 120 and 129 milliseconds no difference in mortality was reported (14.5% compared with 13.2% HR 1.01 [95% CI 0.35 to 2.90]). The Assessment Group highlighted that the subgroup interaction was not statistically significant

($p=0.33$) and these analyses also lacked statistical power and should be viewed with caution.

4.2.29 The individual patient data meta-analysis conducted by Cleland et al. (2013) explored the pre-implantation variables that predict response to CRT. It included individual data from 3872 patients from 5 randomised controlled trials (MIRACLE, MIRACLE ICD, CARE-HF, REVERSE and RAFT). To explore the effectiveness of CRT, the IPD analysis combined the individual patient data from the CRT-D and CRT-P arms and compared this with combined individual patient data from the ICD and OPT arms of the included trials, that is the control arms. A multivariable regression analysis showed statistically significant interaction between effectiveness of resynchronisation therapy and QRS duration for all-cause mortality ($p=0.0013$) and for the composite outcome of death and heart failure hospitalisation ($p<0.0001$). Further analysis to investigate the relationship between QRS duration and CRT indicated that CRT showed beneficial effect on all-cause mortality in patients with a QRS duration more than 126 milliseconds, but the benefit was statistically significant only in patients with a QRS duration more than 140 milliseconds. Cleland et al. (2013) did not have access to individual patient data from 2 large randomised controlled trials (COMPANION and MADIT-CRT). The Assessment Group noted 6 further randomised controlled trials included in the Assessment Group's systematic review were also not included in the Cleland et al. IPD meta-analysis.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ICD, CRT-P and CRT-D devices, having considered evidence on the nature of arrhythmias and heart failure and the value placed on the benefits of implantable devices by people with these conditions, those who represent them, and

clinical specialists. It also took into account the effective use of NHS resources.

- 4.3.2 The Committee considered the nature of both conditions, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical symptoms associated with arrhythmias and heart failure. The Committee noted that heart failure, if left untreated, is associated with a poor prognosis. It heard from the patient experts that people with heart failure may have breathing difficulties, swelling in the ankles, legs and abdomen, feel very tired, and become mentally less alert; and consequently experience poor quality of life. The Committee heard that people with heart failure also have an increased risk of developing life-threatening ventricular arrhythmias. The Committee heard that people who survive a cardiac arrest, or have a higher risk of sudden death due to ventricular arrhythmia, may live in constant fear of death. Moreover, the side effects of antiarrhythmic treatment, the only alternative to treatment with a defibrillating device, include fatigue which can result in people becoming dependent on their family and carers for day-to-day activities. The patient experts emphasised the negative psychological impact both of living with the condition and of receiving antiarrhythmic treatments. The Committee noted that antiarrhythmic treatment needs to be adjusted frequently for optimal effect and this may be demanding for many people. The Committee also noted that antiarrhythmic treatment can have adverse effects on the thyroid, liver or lungs. The Committee concluded that people with ventricular arrhythmias and people with heart failure have a significantly reduced quality of life and an increased risk of death.
- 4.3.3 The Committee heard from the clinical specialists that ICDs have been shown to be superior to pharmacological therapy in people who have survived a cardiac arrest or have spontaneous sustained

ventricular arrhythmia with haemodynamic compromise, and further clinical trials in these groups are therefore considered unethical. Because there was no new randomised evidence, the Committee was satisfied that the recommendations in [Implantable cardioverter defibrillators for arrhythmias](#) (NICE technology appraisal guidance 95) about secondary prevention of ventricular arrhythmias did not need to be changed.

4.3.4 The Committee also noted that in NICE technology appraisal guidance 95, ICDs were recommended for prevention of arrhythmic death in patients with certain familial conditions associated with high risk of sudden cardiac death (such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia) and in people who have undergone surgical repair of congenital heart disease. The Committee heard that these conditions are relatively rare and there is no prospect of randomised trials of ICD therapy in these populations. The Committee noted that no additional evidence was presented for these populations for consideration in this appraisal. The Committee heard that the new evidence available since NICE technology appraisal guidance 95 was issued was observational and confirmed the effectiveness of ICDs in preventing sudden death in people with these cardiac conditions. The Committee concluded that the recommendation in NICE technology appraisal guidance 95 regarding familial cardiac conditions and after surgical repair of congenital heart disease did not need to be changed and that the current appraisal should focus on people at risk of sudden cardiac death because of left ventricular dysfunction (heart failure).

4.3.5 The Committee then discussed the clinical characteristics of the population likely to benefit from ICD therapy for the primary prevention of ventricular arrhythmias. The Committee heard from the clinical specialists that reduced left ventricular function (LVEF)

is a significant predictor of risk of ventricular arrhythmia. It heard that the degree of left ventricular dysfunction is sometimes useful to guide ICD therapy, particularly in patients with a normal QRS duration (see section 4.3.17), but the measurement of LVEF in clinical practice is often imprecise. The Committee further heard from clinical specialists that a threshold of an LVEF of less than 35% is an important indicator, but further categorisation using this measure is generally not used in routine clinical practice. The Committee heard from the clinical specialists that other risk factors like non-sustained ventricular tachycardia on Holter monitoring, and ventricular tachycardia induced by electrophysiological testing have limited sensitivity or specificity for predicting response to ICD implantation and are no longer routinely used in clinical practice. The Committee also understood from the clinical specialists that damage to heart muscle (myocardium) predisposes patients to the risk of arrhythmia and although the extent of myocardial damage is an important consideration, the aetiology (ischaemic or non-ischaemic) does not influence the effectiveness of ICD therapy. The Committee further heard from clinical specialists that prolonged QRS duration and the presence of LBBB on ECG confirms an increased risk of sudden cardiac death. The Committee concluded that some of the stipulations in NICE technology appraisal guidance 95, including history of previous myocardial infarction, presence of non-sustained ventricular tachycardia on Holter monitoring and inducible ventricular tachycardia on electrophysiological testing are no longer used in clinical practice for making decisions on the use of ICD therapy.

- 4.3.6 The Committee then discussed the clinical characteristics of people with heart failure likely to benefit from cardiac resynchronisation therapy (CRT-D and CRT-P), and treatment pathways in this population. The Committee heard from the clinical specialists that heart failure is initially treated with pharmacological therapy,

typically consisting of angiotensin-converting enzyme inhibitors, beta blockers and aldosterone antagonists, for at least 3 to 6 months before device implantation is considered. The Committee heard that CRT devices are indicated in people who have an LVEF of less than 35% and have heart failure symptoms despite receiving optimal pharmacological therapy. The Committee heard that CRT has a beneficial effect on patients with symptomatic heart failure with evidence of increased ventricular activation time (that is, prolonged QRS duration) or dyssynchrony (presence of LBBB) on ECG. The clinical specialists clarified that other measures such as mechanical dyssynchrony are no longer considered clinically useful.

- 4.3.7 The Committee also noted that CRT devices were not recommended for patients in NYHA classes I and II in [Cardiac resynchronisation therapy for the treatment of heart failure](#) (NICE technology appraisal guidance 120) and heard from clinical specialists that it is more appropriate to use the therapy in patients with more severe symptoms (that is, NYHA class III or IV) because it alleviates heart failure symptoms. The Committee asked the clinical specialists about the validity of classification based on NYHA criteria, noting that it is based on assessment of symptoms which may be subjective. The Committee heard that NYHA class I (no symptoms) and class IV (symptomatic at rest) are generally demarcated easily, but there is more likely to be overlap in the definitions of NYHA classes II and III. The Committee also heard that NYHA classification was in use in clinical practice, had been used in the trials, and was considered an important prognostic marker in heart failure. The Committee concluded that, based on current standard practice in the UK, severity of symptoms (NYHA class), duration of QRS complex and the presence or absence of LBBB are important clinical characteristics for identifying patients who are likely to benefit from CRT devices.

4.3.8 The Committee discussed the adverse events associated with implantable devices. The Committee was aware that implantation procedures are associated with adverse events, but heard that improvements in the quality of the devices and operator skills have resulted in a decline in adverse event rates during implantation. It heard from the patient experts that the shocks delivered by defibrillator devices (ICD and CRT-D) may cause anxiety and have an adverse effect on quality of life. However, the Committee also heard that the reassurance that patients with defibrillators experience generally outweighs any disadvantages associated with shocks. The Committee also heard from clinical specialists that improvement in the algorithm for detection of arrhythmia and in the discrimination between physiological and pathological tachycardia, has reduced the incidence of inappropriate shocks. The Committee noted that patients with a defibrillator device have driving and employment restrictions, further affecting their quality of life. The patient experts and the clinical specialists emphasised the importance of pre- and post-placement counselling as well as access to counselling after defibrillator shocks, in maximising the benefits from device implantation. The Committee heard from the patient experts that comprehensive information about the condition, available treatment options, the differences between the devices and the risks of implantation is extremely important to enable people to make informed choices about therapy. The patient experts also stated that patients should be given information before implantation on expected outcomes, living with the device and having it switched off in old age. The Committee noted consultation comments that deactivation of defibrillators is a simple non-invasive re-programming process, and heard that it was important, after appropriate consultation and counselling with patients and their families, to deactivate implanted devices to prevent patients receiving painful and futile shocks at the end of their lives. The

Committee agreed with the views of the clinical specialists and patient experts that careful, explicit and shared decision-making about appropriate use of these technologies in the context of end-of-life care planning is important.

- 4.3.9 The Committee discussed the evidence base available for the effectiveness of ICDs, CRT-P and CRT-D compared either with medical therapy or with each other. The Committee noted that the systematic reviews conducted by the Assessment Group and the manufacturers identified largely the same trial evidence. The Committee was aware that the manufacturers' submission excluded trials evaluating ICDs for secondary prevention and noted that this was appropriate for the specific focus of this appraisal (see section 4.3.4). The Committee noted that different approaches were taken by the Assessment Group and the manufacturers for synthesising the results (see section 4.1.1). The Committee considered the results presented in the assessment report and noted that patients receiving ICDs had lower risk of sudden cardiac death than patients receiving medical therapy across all the trials. The Committee also noted that implantation of ICDs for prevention of ventricular arrhythmia decreased all-cause mortality and cardiac mortality in people with mild to moderate heart failure or in those who had a previous history of myocardial infarction. The Committee also noted that the benefits of implantation of a CRT device are related to improvements in the symptoms of heart failure (NYHA class and 6-minute walking distances) and health-related quality of life, and a reduction in the deaths due to heart failure. The Committee then considered the results of the IPD NMA conducted by the manufacturer and noted that compared with optimal pharmacological therapy, devices (ICD, CRT-P and CRT-D) were associated with favourable outcomes. The Committee also noted that some patient characteristics, such as age, sex, QRS duration and LBBB, were predictors of benefit from the different devices

(effect modifiers). The Committee also noted that results of the 2 analyses were largely consistent and the use of implantable devices was associated with favourable outcomes compared with medical therapy. The Committee concluded that in general, ICD, CRT-D and CRT-P devices were effective in improving survival and health-related quality of life in people with heart failure.

4.3.10 The Committee then considered which of the 2 available analyses were more appropriate for its decision-making, the manufacturers' IPD NMA and associated economic modelling or the Assessment Group's analyses, noting that the latter were more aligned with the scope of the appraisal and based on published data. However, the Committee was aware of comments received during consultation on the assessment report that there were no clinical criteria that allowed most of the trials in this review to be related specifically to the groups defined in the scope. The Committee considered that the individual patient data available from approximately 12,500 patients, including around 95% of the patients included in studies identified in the systematic review, was a rich and important data source. The Committee also noted that the approach taken by the manufacturers allows consideration of population groups based on clinical characteristics that are considered important by clinicians in current clinical practice for making decisions about device implantation. The Committee concluded that, in this instance, results from the IPD NMA should be used to inform the economic modelling.

4.3.11 The Committee discussed the uncertainties in the manufacturers' IPD NMA. The Committee was aware that the IPD NMA has not yet been published and therefore lacked the benefit of peer review. However, the Committee noted that the results, where comparable, were largely consistent with the Assessment Group's analyses carried out at study level. The Committee noted that trials included

were heterogeneous in terms of baseline patient characteristics, length of follow-up and pharmacological therapy, but acknowledged that the meta-regression approach allowed for baseline heterogeneity to be taken into account in evaluating the effectiveness of the devices. However, the Committee noted that heterogeneity introduced by different pharmacological treatment and different length of follow-up across the trials had not been explored. The Committee also noted that some patient groups such as those in NYHA classes I and IV and women were under-represented in the analyses. The Committee heard from the clinical specialists that in general, patients in the trials were about 10 years younger than the average age of people with heart failure in the UK, although the Committee also noted that the age of patients in the trials was comparable with that of people in the UK who receive devices. The Committee noted that some subgroups defined by clinical covariables were very small, which led to uncertain results. The Committee also discussed the improvement of pharmacological treatment over time and whether it could affect treatment effectiveness associated with devices. It heard from the clinical specialists that treatment of heart failure has improved considerably with the availability of medicines such as angiotensin-converting enzyme inhibitors. It also heard from the patient experts that initiatives such as care by heart failure specialist nurses had resulted in improved compliance. Because of that, the Committee concluded that treatment effects derived from older trials could be overestimated and that results should be interpreted with caution. The Committee also noted that both relative treatment effects and baseline risk in the manufacturers' model were based on the IPD NMA, whereas the baseline risk should ideally be inferred from data relating to routine use. The Committee concluded that the considerable uncertainties needed to be taken into account when

deciding whether the technologies represented an acceptable use of NHS resources.

- 4.3.12 Having concluded that the manufacturers' IPD NMA and economic model would inform its decision-making, the Committee discussed whether there were any key points from the Assessment Group's approach that should also be taken into consideration. It noted that the Assessment Group's model allowed for device crossover, that is, patients initially receiving pharmacological therapy could receive a device on disease progression, and patients with a device could have an upgrade if clinically appropriate. The Committee also noted that observational data as well as clinical specialist opinion, including clinical input received by the Assessment Group, indicated that device upgrades are not common in clinical practice. The Committee therefore concluded that the manufacturers' approach excluding crossover was appropriate for this appraisal.
- 4.3.13 The Committee then discussed the key assumptions in the manufacturers' model. The Committee heard from the manufacturers that the constant mortality benefit of 7.5 years assumed in the base case was the maximum duration of follow-up in the IPD. The Committee was concerned about the validity of this assumption, noting that the IPD NMA included outcome data observed over protocol-specified data-lock periods in the individual trials. It noted that the duration of the data-lock period across the trials ranged from 3 to 41 months and average duration was 2.54 years, substantially lower than the 7.5 years assumed in the model. The Committee also noted the manufacturers' comment that analysis from the IPD NMA suggested that the treatment effects on all-cause mortality did not vary over time. When considering the analyses based on alternative assumptions the Committee agreed that a constant mortality benefit of 2.54 years may be too pessimistic but that 7.5 years was too optimistic. It also noted that

the modelling of device effectiveness for all-cause mortality differed from that for health-related quality of life, in that a constant health-related quality of life benefit was applied for 5 years before tapering. The Committee noted that long-term follow-up data from the CARE-HF trial showed that treatment effects of CRT-P were maintained at around 4 years despite crossover, which was consistent with the Committee's preferred assumption. The Committee was also aware that long-term data from MADIT-II indicated that effects of ICDs were maintained at around 7.5 years despite crossover. However, the Committee concluded that this would not necessarily apply to CRT devices.

- 4.3.14 The Committee noted that after the constant effect period, the modelling included tapering (a gradual linear decrease) of the effectiveness up to 20 years. The manufacturers stated that this assumption was more conservative than the assumption used in the models informing the NICE technology appraisal guidance 95 and NICE technology appraisal guidance 120 recommendations which did not include any tapering effect. However, the Committee noted that in the current appraisal the manufacturer had modelled treatment effect of the devices on all-cause mortality, making tapering essential because the risk of mortality would increase with age due to other factors, whereas in the previous models tapering was implicit because constant treatment effect was applied to disease-specific mortality from arrhythmia or worsening of heart failure. The Committee therefore did not consider the current approach including tapering to be necessarily more conservative. The Committee was aware that assuming no benefit after the duration of constant effect or assuming a more rapid decline of effectiveness increased the ICERs in the Assessment Group's exploratory sensitivity analyses. Without any evidence to indicate that these alternative assumptions were more appropriate, the Committee saw no reason to deviate from the manufacturers'

assumption of tapering up to 20 years. The Committee maintained that, on balance, a constant mortality benefit for 5 years followed by tapering up to 20 years would be the most reasonable assumption.

4.3.15 The Committee noted that the base-case ICERs were not particularly sensitive to alterations in most cost parameters, including counselling costs. The Committee was however, concerned that the combined effect of uncertainty had not been explored in a probabilistic sensitivity analysis and heard that this was because, given the nature of the data, it would have taken several months to run it across all patient profiles. However, the Committee concluded that the absence of probabilistic sensitivity analyses made it more difficult to allow for uncertainty when reaching decisions about the cost effectiveness of the devices. The Committee discussed the results of the manufacturers' analyses for 24 subgroups after combining the ischaemic and non-ischaemic subgroups, based on its preferred assumption of constant mortality benefit being maintained for 5 years followed by tapering up to 20 years. It noted that the 4 subgroups with the combination of LBBB and a QRS duration of less than 120 milliseconds were clinically implausible because LBBB cannot occur with a normal QRS duration (less than 120 milliseconds). In addition, there was 1 subgroup (NYHA class IV, QRS duration less than 120 milliseconds, without LBBB) in which no device was evaluated. The Committee concluded that the ICERs based on fully incremental analyses and the predicted optimal strategies for the remaining 19 subgroups were an appropriate basis for making recommendations.

4.3.16 The Committee discussed the cost-effectiveness results in the 3 subgroups with a normal QRS duration (less than 120 milliseconds) across NYHA classes I, II and III. The Committee noted that ICDs were compared with OPT and were associated

with ICERs between £25,000 and £30,000 per QALY gained. Having heard of the distress caused by shocks from ICDs, the Committee queried whether ICDs were used in practice for asymptomatic people (that is, NYHA class I) with a QRS duration of less than 120 milliseconds. The Committee heard that patients would have been symptomatic at presentation with heart failure but would have become classified as NYHA class I as a result of optimal pharmacological therapy. Taking into consideration the uncertainties of evidence synthesis identified in section 4.3.12, and the lack of a full exploration of parameter uncertainty in the model (section 4.3.16), the Committee debated whether ICDs were a cost-effective option in these subgroups. The Committee noted comments from consultation that the clinical evidence does not support restricting the use of ICDs in patients with a normal QRS duration. The Committee heard from the clinical specialists that some patients with normal QRS duration are at high risk of sudden death and that it was important to have treatment options available for this population.

- 4.3.17 The Committee then explored the approaches used by clinical specialists in defining high risk in people with normal QRS duration. The Committee heard that while age and sex were regarded as important considerations in assessing risk of sudden cardiac death, and correspondingly inform the indication for ICD, these are not the only factors used in clinical practice. Other factors may include the degree of left ventricular dysfunction, history of myocardial infarction including the extent and location of myocardial damage (particularly the presence of a large anterior infarct), and presence of cardiomyopathy. In addition, a range of other potential prognostic factors may be used, like B-type natriuretic peptide. The Committee also noted consultation comments suggesting that most patients with normal QRS would require only a single chamber ICD which has a lower cost and greater battery longevity than conventional

dual chamber ICDs. The Committee heard that the model included the average cost of all ICDs sold to the NHS in a year, which may therefore have overestimated the costs for ICD for some people in these subgroups. Taking into account the high burden of premature deaths in these subgroups, the Committee was persuaded to recommend ICDs in patients with a LVEF less than 35% with a normal QRS duration (less than 120 milliseconds) with NYHA class I, II and III symptoms, who are considered to be at high risk of sudden cardiac death.

4.3.18 The Committee noted that the manufacturers did not evaluate any device (ICD, CRT-D or CRT-P) in the subgroup with a normal QRS duration (less than 120 milliseconds) and with NYHA class IV symptoms. The Committee also noted that very limited data were available for this subgroup from the manufacturers' IPD NMA. The Committee heard that CRT devices are only indicated in patients with prolonged QRS duration and that ICDs are not suitable in severely symptomatic patients due to the risk of frequent defibrillator shocks. The Committee also noted that ICDs were not recommended for patients with severe symptoms of heart failure (NYHA class IV) in NICE technology appraisal guidance 95. The Committee was therefore satisfied that it is reasonable not to evaluate ICD or CRT devices in this subgroup.

4.3.19 The Committee then discussed the cost-effectiveness results for the 4 subgroups with NYHA class IV, a QRS duration of more than 120 milliseconds and with or without LBBB. It noted that OPT, CRT-P and CRT-D were compared in a fully incremental analysis. ICDs were excluded from the analyses based on clinical opinion. The Committee noted that patients in NYHA class IV have severe symptoms, poor quality of life and limited life expectancy. The Committee heard that alleviation of heart failure symptoms is the main goal for these people and defibrillator devices may worsen

quality of life because of defibrillator shocks. The Committee agreed that, because of this, like ICDs, CRT-D should also not be used in these subgroups. The Committee noted that the comparison of CRT-P with OPT resulted in ICERs ranging from £14,000 to £23,000 per QALY gained, depending on QRS duration and the presence or absence of LBBB. The Committee concluded that CRT-P is a cost-effective treatment option for people in NYHA class IV with a prolonged QRS duration (more than 120 milliseconds), both with and without LBBB.

4.3.20 The Committee discussed whether resynchronisation therapy was appropriate in the subgroups with a QRS duration between 120 and 149 milliseconds. The Committee heard from the clinical specialists that a recently published trial (EchoCRT, Ruschitzka et al. 2013) reported that in patients with QRS durations of less than 130 milliseconds, prognosis could be adversely affected with CRT devices. The Committee also heard that another recently published, individual patient meta-analysis study reported that the clinical benefit of CRT in patients with QRS durations between 120 and 140 milliseconds was smaller and less certain than those with a longer QRS duration (Cleland et al. 2013). The Committee noted that the Cleland et al. study demonstrated a significant interaction between CRT and QRS duration for mortality as well as for the composite endpoint of mortality and morbidity. In addition, the relationship between the effect of CRT and QRS duration as a continuous variable showed a progressive increase in the benefit of CRT as QRS duration increased, with a statistically significant mortality benefit in patients with a QRS duration of more than around 140 milliseconds. It also indicated that CRT could have a potentially harmful effect in patients with a QRS duration less than 126 milliseconds. The Committee noted comments that Cleland et al. study did not include a sizeable number of patients from other relevant trials, the proportion of patients within the narrow QRS

range was very small and that considering improvement in symptoms was as important as mortality benefits. However, the Committee was concerned that the population with a QRS duration between 120 and 149 milliseconds is heterogeneous and included some patients in whom CRT may be inappropriate. The Committee considered that further categorisation based on QRS duration would be needed to identify subgroups that may benefit from resynchronisation and noted that this was not presented, although the analysis would be possible using the manufacturers' IPD NMA. The Committee heard from the clinical specialists that in clinical practice CRT devices are usually considered in patients with a QRS duration of more than 130 milliseconds, and often more than 140 milliseconds. The clinical specialists also stated that for subgroups with intermediate QRS, most benefit with CRT occurs in patients with LBBB. The manufacturers also stated that the IPD NMA suggested that the proportion of patients with LBBB increased with increase in QRS duration. The Committee heard from clinical specialists that the presence of LBBB provided confirmation of the presence of dyssynchrony and therefore potential for benefit from CRT therapy. The Committee concluded that, without more robust analysis, it is appropriate to take a cautious approach to the use of CRT in this intermediate QRS group.

- 4.3.21 The Committee discussed the results for patients with a QRS duration between 120 and 149 milliseconds and NYHA class I or II symptoms. Based on the manufacturers' analysis it noted that, for the 2 subgroups without LBBB, ICDs were presented as the optimal strategy, with ICERs of approximately £17,000 per QALY gained compared with OPT. For those in NYHA class I or II with LBBB, however, the Committee noted that CRT-D was presented as the optimal strategy. Following the discussion in section 4.3.20 regarding potential harm with CRT in patients with a slightly

prolonged QRS duration, the Committee considered that CRT-D could not be clearly recommended for people in NYHA class I because there is less potential for symptomatic benefit and instead took into consideration the ICERs for ICDs when CRT-D was excluded. The Committee noted that the ICER for ICDs compared with OPT was approximately £22,000 per QALY gained for NYHA class I with LBBB. For NYHA class II with LBBB, the Committee took into consideration comments from consultation that NYHA class II is often difficult to distinguish from NYHA class III. In this scenario, the Committee considered that some degree of symptomatic impact (NYHA class II) with LBBB provides confirmation of the presence of dyssynchrony and therefore the potential to benefit from CRT. The Committee concluded, given unresolved concerns about the balance of benefits and harms with CRT devices, that within the QRS categories presented in the manufacturers' analyses, ICDs are a cost-effective treatment option in patients in NYHA class I with a QRS duration between 120 and 149 milliseconds, both with and without LBBB; and in patients in NYHA class II with a QRS duration between 120 and 149 milliseconds without LBBB. It further concluded that CRT-D is a cost-effective treatment option in patients in NYHA class II with a QRS duration between 120 and 149 milliseconds with LBBB.

4.3.22 The Committee then discussed the results for the 2 subgroups including people in NYHA class III with QRS duration between 120 and 149 milliseconds. It noted that CRT-D was presented as the optimal strategy for the subgroups with and without LBBB. In line with section 4.3.20, the Committee noted that CRT-D would not be recommended for these subgroups. However, the clinical specialists stated that for the subgroup with LBBB, CRT-D is widely used in clinical practice and the presence of LBBB provides confirmation of the presence of dyssynchrony and therefore potential for benefit from CRT. Taking into account the severity of

symptoms of NYHA class III patients and the potential for improvement with resynchronisation therapy, the Committee was persuaded that for this subgroup it was appropriate to consider CRT. The Committee noted that the ICER for CRT-D compared with CRT-P in this subgroup was approximately £26,000 per QALY gained and the ICER for CRT-P compared with OPT was approximately £14,000 per QALY gained. The Committee was aware of the uncertainties surrounding the ICERs, but considered that given the severity of the symptoms and the clinical plausibility of benefit from CRT-D, the ICER was acceptable. For the subgroup without LBBB, the Committee excluded CRT from consideration and noted that the ICER for ICDs compared with OPT would be around £24,000 per QALY gained. The Committee concluded that for people in NYHA class III, with QRS duration between 120 and 149 milliseconds, ICDs could be considered cost effective in the subgroup without LBBB and CRT-D or CRT-P could be considered cost effective in the subgroup with LBBB.

4.3.23 The Committee discussed the 4 subgroups of people in NYHA classes I and II with a prolonged QRS duration of 150 milliseconds or more, both with and without LBBB. The Committee was aware that QRS duration of more than 150 milliseconds indicates cardiac dyssynchrony and carries an increased risk of death from arrhythmia. The Committee noted that OPT, ICDs and CRT-D were evaluated in these subgroups and CRT-D was presented as the optimal strategy with ICERs compared with ICDs ranging from £18,000 to £25,000 per QALY gained. The Committee concluded that CRT-D could be considered cost effective in people in NYHA classes I and II, with a QRS duration of more than 150 milliseconds, both with and without LBBB.

4.3.24 The Committee discussed the results in patients in NYHA class III with QRS duration of 150 milliseconds or more and with, or without,

LBBB. It noted that in the subgroup without LBBB, CRT-D was presented as the optimal strategy with an ICER of approximately £26,000 per QALY gained compared with CRT-P. As discussed previously, given the severity and nature of the disease in this group of people, the Committee considered that the uncertainty around the ICERs was acceptable. For the subgroup with LBBB the Committee noted that CRT-P was presented as the optimal strategy because the ICER for CRT-D compared with CRT-P was slightly above £30,000 per QALY gained. The Committee noted the consultation comments that it would be clinically counter-intuitive not to recommend CRT-D in this patient group when CRT-D was recommended in patients in lower risk categories (that is, without LBBB) as well as in patients with milder symptoms of heart failure (NYHA classes I and II). The Committee noted that patients in this group were severely symptomatic and at high risk of sudden cardiac death and have the most potential to benefit from a CRT-D device. Because of the value placed on the benefits of CRT-D in this patient group, the Committee concluded that it was justified to accept an ICER of just above £30,000 per QALY gained. The Committee therefore concluded that for people in NYHA class III, with QRS duration more than 150 milliseconds with or without LBBB, both CRT-D and CRT-P could be considered cost effective.

Summary of Appraisal Committee’s key conclusions

TAXXX	Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of NICE technology appraisals 95 and 120)	Section
Key conclusion		
The Committee looked at 20 subgroups of patients for all combinations of NYHA class, QRS duration and presence of LBBB. Fully incremental ICERs for the devices, using the Committee’s preferred assumptions, were available and the Committee also took modifying factors, such as severity of the condition and the risk of harm into consideration. The plausible ICERs for the respective recommended devices in the subgroups were between £11,000 and £31,000 per QALY gained. Please see table 1 for the recommendations for each subgroup.		1.2

<p>The Committee also concluded that the recommendation in NICE technology appraisal guidance 95 regarding previous serious ventricular arrhythmia, certain familial cardiac conditions and after surgical repair of congenital heart disease did not need to be changed.</p>		<p>1.1 4.3.3, 4.3.4</p>
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the patient experts that people with heart failure may have breathing difficulties, swelling in the ankles, legs and abdomen and severe tiredness. They may become less mentally alert; and consequently experience poor quality of life. The Committee also heard that people who have a higher risk of ventricular arrhythmia may live in constant fear of sudden death. Antiarrhythmic drug treatment needs to be adjusted frequently which may be demanding for many patients, and the side effects of antiarrhythmic treatment include fatigue which can result in people becoming dependent on their family and carers for day-to-day activities. The Committee also noted that antiarrhythmic treatment can have adverse effects on the thyroid, liver or lungs. The Committee concluded that people with ventricular arrhythmias and people with heart failure have a significantly reduced quality of life and an increased risk of death.</p>	<p>4.3.2</p>
<p>The technology</p>		
<p>Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee noted that the use of implantable devices was associated with favourable outcomes compared with medical therapy and in general, ICD, CRT-D and CRT-P devices were effective in improving survival and health-related quality of life in people with heart failure.</p> <p>No claim for innovation was presented to the Committee.</p>	<p>4.3.9</p>

What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical specialists that reduced left ventricular function is a significant predictor of risk of sudden cardiac death in patients with heart failure, and prolonged QRS duration and the presence of LBBB further increase the risk.	4.3.5
	The Committee heard that CRT devices are indicated in people who have an LVEF of less than 35% and have heart failure symptoms despite receiving optimal pharmacological therapy, with beneficial effects particularly in people with prolonged QRS duration or presence of LBBB.	4.3.6
	The Committee heard from the clinical specialists that patients in NYHA class IV have severe symptoms, poor quality of life and limited life expectancy. The Committee heard that alleviation of heart failure symptoms is the main goal for these people and defibrillator devices may worsen quality of life because of defibrillator shocks.	4.3.19
	The Committee agreed with the views of the clinical specialists and patient experts that careful, explicit and shared decision-making about appropriate use of these technologies in the context of end-of-life care planning is important.	4.3.5
Adverse reactions	The Committee heard that the shocks delivered by defibrillator devices (ICD and CRT-D) may cause anxiety and have an adverse effect on quality of life. The Committee was aware that implantation procedures are associated with adverse events, but heard that improvements in the quality of the devices and operator skills have resulted in a decline in adverse event rates during implantation.	4.3.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The systematic reviews conducted by the Assessment Group and the manufacturers identified largely the same trial evidence. Different approaches were taken by the Assessment Group and the manufacturers for synthesising the results.	4.3.9
	The Committee considered that the individual patient data available from approximately 12,500 patients, which covered around 95% of the patients included in studies identified in the systematic review, was a rich and important data source and agreed that results from the IPD NMA should be used to inform the economic modelling.	4.3.10

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The manufacturers' NMA indicated that age, sex, QRS duration and LBBB status independently predicted the magnitude of benefit on all-cause mortality associated with the devices.</p> <p>For patients with a normal QRS duration the Committee explored the approaches used in clinical practice in identifying patients at a high risk of sudden cardiac death to inform decisions about ICD implantation. The Committee heard that age, sex, degree of left ventricular dysfunction, history of myocardial infarction, presence of cardiomyopathy and a range of other potential prognostic factors like B-type natriuretic peptide may be used.</p> <p>The Committee was concerned that recent studies suggested that the subgroups with a QRS duration between 120 and 149 milliseconds were heterogeneous, containing some patients in whom CRT may be inappropriate.</p>	<p>4.1.40</p> <p>4.3.17</p> <p>4.3.19</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee noted that the systematic reviews conducted by the Assessment Group and the manufacturers identified largely the same trial evidence and the results of the 2 analyses were largely consistent.</p> <p>The Committee considered that the individual patient data available from approximately 12,500 patients, included in the manufacturers' analysis, was a rich and important data source.</p> <p>The results from the manufacturers' IPD NMA are academic in confidence.</p> <p>The Committee concluded that in general, ICD, CRT-D and CRT-P devices were effective in improving survival and health-related quality of life in people with heart failure.</p>	<p>4.3.9</p> <p>4.3.10</p> <p>4.1.40</p> <p>4.3.9</p>

<p>For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisals (TA95 and TA120) influenced the current recommendations?</p>	<p>The Committee concluded that some of the stipulations in TA95, including history of previous myocardial infarction, presence of non-sustained ventricular tachycardia on Holter monitoring and inducible ventricular tachycardia on electrophysiological testing are no longer used in clinical practice for making decisions on the use of ICD therapy.</p> <p>The clinical specialists clarified that measures such as mechanical dyssynchrony (described in TA120) are not considered clinically useful.</p> <p>The Committee concluded that, based on current standard practice in the UK, severity of symptoms (NYHA class), duration of QRS complex and the presence or absence of LBBB are important clinical characteristics for identifying patients who are likely to benefit from CRT devices.</p>	<p>4.3.5</p> <p>4.3.6</p> <p>4.3.7</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The Assessment Group presented cost-effectiveness results for each of the 3 populations outlined in the scope, whereas the manufacturers modelled the individual patient data for 12,638 patients, splitting them into subgroups according to NYHA class, QRS duration, LBBB status and aetiology of heart disease, and reported cost-effectiveness results for each subgroup.</p> <p>The Committee noted that the approach taken by the manufacturers allows consideration of population groups based on clinical characteristics that are considered important by clinicians in making decisions about device implantation.</p>	<p>4.2.1</p> <p>4.3.10</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee agreed that the duration of constant mortality benefit of 7.5 years was too optimistic because average duration across the trials was 2.54 years. The Committee noted the discrepancy between the modelling of device effectiveness in terms of all-cause mortality and health-related quality of life, in that a constant health-related quality of life benefit was applied for 5 years before tapering.</p> <p>The Committee noted that the base-case ICERs were not particularly sensitive to alterations in most cost parameters, including counselling costs. The Committee was concerned that the combined effect of uncertainty had not been explored in a probabilistic sensitivity analysis and concluded that the absence of probabilistic sensitivity analyses made it more difficult to allow for uncertainty when reaching decisions about the cost effectiveness of the technologies.</p>	<p>4.3.13</p> <p>4.3.15</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The manufacturers' model assumed that the health-related quality of life benefit from a device would be maintained for 5 years and thereafter would decrease in a linear manner so that there would be no additional benefit after 10 years.</p> <p>No</p>	<p>4.2.16</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The base case deterministic results were presented for 20 subgroups defined by NYHA class, QRS duration and LBBB status, highlighting the most cost-effective treatment strategy at a maximum acceptable ICER of £30,000, £25,000 and £20,000 per QALY gained for each subgroup.</p>	<p>4.2.17</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The manufacturers' base-case ICERs for the devices were most sensitive to changes to the assumptions regarding the magnitude of treatment effect on mortality, duration of constant effect and the duration for which the tapering effect was applied.</p>	<p>4.2.18,</p> <p>4.2.23</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee discussed the results of the manufacturers' analyses for 20 subgroups after combining the ischaemic and non-ischaemic subgroups, based on its preferred assumption of constant mortality benefit being maintained for 5 years followed by tapering up to 20 years.</p> <p>The most likely ICERs for the Committee's preferred assumptions are presented in table 2 in the evidence section. The most plausible ICERs for the respective recommended devices in the subgroups were between £11,000 and £31,000 per QALY gained.</p>	<p>4.3.15</p> <p>4.2.18</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>N/A</p>	
<p>End-of-life considerations as per the supplementary advice for treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses</p>	<p>N/A</p>	
<p>Equalities considerations and social value judgements</p>	<p>Potential equality issues raised during the appraisal were outside the remit of NICE technology appraisal guidance.</p>	

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has increased risk of ventricular arrhythmias and/or heart failure and the doctor responsible for their care thinks that implantable cardioverter therapy or cardiac resynchronisation therapy is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.3 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below).

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Insertion of a subcutaneous implantable cardioverter defibrillator for prevention of sudden cardiac death](#). NICE interventional procedure guidance 454 (2013).
- [Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care](#). NICE clinical guideline 108 (2010).

- [Cardiac resynchronisation therapy for the treatment of heart failure](#). NICE technology appraisal guidance 120 (2007).
- [Implantable cardioverter defibrillators for arrhythmias](#). NICE technology appraisal guidance 95 (2006).

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in May 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Ken Stein

Vice Chair, Appraisal Committee

April 2014

8 Appraisal Committee members and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Matthew Campbell-Hill

Lay member

Dr Lisa Cooper

Echocardiographer, Stockport NHS Foundation Trust

Dr Maria Dyban

General Practitioner

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Robert Hinchliffe

HEFCE Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

Dr Neil Iosson

General Practitioner

Anne Joshua

Associate Director of Pharmacy, NHS Direct

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Terence Lewis

Lay member

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research

National Institute for Health and Care Excellence

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Final appraisal determination – implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120)

Issue date: April 2014

at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Christopher O'Regan

Head of Health Technology Assessment and Outcomes Research, Merck Sharp and Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay member

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Cliff Snelling

Lay member

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

9 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Anwar Jilani

Technical Lead

Raisa Sidhu

Technical Adviser

Jeremy Powell

Project Manager

10 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- Colquitt JI, Mendes D, Clegg AJ et al., Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation, January 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Manufacturers/sponsors:

- Biotronik UK
- Boston Scientific
- Medtronic UK
- Sorin Group
- St Jude Medical UK

II. Professional/specialist and patient/carer groups:

- Arrhythmia Alliance
- British Association for Nursing in Cardiovascular Care
- British Cardiovascular Society
- British Heart Foundation
- Heart Rhythm UK
- Primary Care Cardiovascular Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- SADS UK

III. Other consultees:

- Department of Health
- Welsh Assembly Government

IV. Commentator organisations (without the right of appeal):

- Actavis UK
- Association of British Healthcare Industries
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on implantable cardioverter defibrillators and cardiac resynchronisation therapy by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Wendy Churchouse, BNF Arrhythmia Specialist Nurse, nominated by the Royal College of Nursing – clinical specialist
- Dr Roy Gardner, Consultant Cardiologist, nominated by the British Society for Heart Failure – clinical specialist
- Dr Chris Plummer, Consultant Cardiologist, nominated by Heart Rhythm UK – clinical specialist
- Caroline Holmes, Senior Associate, Patient Services at Arrhythmia Alliance nominated by Arrhythmia Alliance – patient expert

D. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. They were also invited to comment on the ACD.

- Biotronik UK
- Boston Scientific
- Medtronic UK
- Sorin Group
- St Jude Medical UK