Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final Protocol

5th December 2011

1. Title of the project:

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

HTA reference 10/109/01

2. Name of TAR team and 'lead'

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3. Plain English Summary

Arrhythmias occur when the heart contracts irregularly or at a faster or slower pace than normal. One type of arrhythmia is a ventricular arrhythmia, which is triggered by the lower chambers of the heart (the ventricles) and can cause sudden death. There are many different causes of ventricular arrhythmias but they most commonly happen in people who already have heart disease.[1] For young people with no history of heart disease, the National Audit of Sudden Arrhythmic Death 2010[2] identified 86 sudden cardiac deaths among 283 deaths referred to UK Cardiac Pathology Network (CPN) pathologists that occurred between the launch of the database in November 2008 until October 2010. This audit[2] also states that most sudden deaths in people under 30 years of age are caused by cardiomyopathies and arrhythmias that have a genetic basis (i.e. they are inherited). Drugs may be used to suppress the development of arrhythmias, but these are not able to stop an arrhythmia once it has started. An additional option is a small electronic device called an implantable cardioverter defibrillator (ICD), which is placed into the upper chest. The device reduces the risk of sudden death by controlling the pace of the heartbeat, sensing for an irregular heartbeat and if necessary delivering shocks to the heart to return it to a normal rhythm (defibrillate).

In heart failure the heart does not work as efficiently as it should. Heart failure affects at least 1% of people in the UK, a proportion that increases steeply with age to about 7% of men and women over 75 years.[3] The National Heart Failure Audit for the period April 2009 to March 2010 reported that 32% of heart failure patients died within the year of admission for heart failure.[3] Heart failure may be treated with drugs, but as the condition worsens these may no longer control symptoms. When the heart is weakened and not working as efficiently as it should [left ventricular systolic dysfunction (LVSD)] there can be additional problems related to the coordination of the heart beat and dyssynchronous contraction. An additional treatment is cardiac resynchronisation therapy (CRT). This involves a small electronic pacing device (CRT-P) which is put into the upper chest with wires within the heart to coordinate heart contraction and thereby improve heart function.

People with heart failure due to LVSD are also at risk from sudden cardiac death due to ventricular arrhythmia. However, not all will actually experience an arrhythmia. Those at greatest risk of experiencing an arrhythmia may benefit from a CRT device that can also defibrillate the heart (CRT-D).

The National Institute for Health and Clinical Excellence (NICE) has previously approved the use of ICDs for certain categories of patients with arrhythmia (TA95) and the use of CRT-P

for people with heart failure and meeting certain criteria (TA120). The use of CRT-D has been approved for people who fulfil criteria for both an ICD and a CRT-P.

This project will systematically summarise the results of clinical trials that have considered the use of ICDs, CRT-P or CRT-D as a treatment for patients at increased risk of sudden death from ventricular arrhythmia and / or with heart failure, whose symptoms are not controlled by appropriate drug therapy. It will compare the costs, benefits and harms of treatment with these devices from an NHS perspective. An independent economic evaluation will be undertaken to estimate the cost-effectiveness of these devices. This will help NICE to determine whether the devices represent an efficient use of resources and to update the recommendations on the use of these devices (previously considered separately in NICE guidance documents TA95 and TA120).

4. Decision problem

4.1 Rationale for the review

This assessment will update TA95 'Implantable cardioverter defibrillators for arrhythmias' and TA120 'Cardiac resynchronisation therapy for the treatment of heart failure' and will report the evidence for clinical-effectiveness and cost-effectiveness in a single Multiple Technology Appraisal.

4.2 Decisions to be made

The aims of this health technology assessment are threefold:

1. to assess the clinical-effectiveness and cost-effectiveness of ICDs in addition to optimal pharmacological therapy for the treatment of people who are at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite receiving optimal pharmacological therapy;
2. to assess the clinical-effectiveness and cost-effectiveness of CRT-P or CRT-D in addition to optimal pharmacological therapy for the treatment of people with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving optimal pharmacological therapy;
3. to assess the clinical-effectiveness and cost-effectiveness of CRT-D in addition to optimal pharmacological therapy for the treatment of people who have both an increased risk of sudden cardiac death as a result of ventricular arrhythmias and heart failure as a result of LVSD and cardiac dyssynchrony despite optimal pharmacological therapy.

4.3 Population and relevant subgroups

There are three groups of people included in this appraisal as noted above.

1. People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite receiving optimal pharmacological therapy. Two common ventricular arrhythmias are ventricular tachycardia, where the ventricles beat too fast and ventricular fibrillation, where the ventricles contract in a chaotic and irregular way. Ventricular arrhythmias commonly occur in the presence of structural heart disease, but can also occur in structurally normal hearts.[1] A UK study found that approximately 40% of sudden cardiac death cases had no prior health service history of cardiac abnormalities or symptoms suggestive of a ventricular arrhythmia.[4] If a life threatening ventricular arrhythmia has already been experienced an ICD may be fitted to treat further episodes thus preventing sudden cardiac death (secondary prevention). Alternatively an ICD may be fitted in someone who has not yet experienced a life-threatening arrhythmia but is deemed to be at risk of experiencing one (primary prevention).
2. People with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving optimal pharmacological therapy. In these people the heart is not acting efficiently as a pump and if symptoms are not controlled by pharmacological treatment a cardiac rhythm device (either CRT-P or CRT-D) may be implanted with the aim of improving cardiac function and heart failure symptoms.
3. People with both an increased risk of sudden cardiac death as a result of ventricular arrhythmias and heart failure as a result of LVSD and cardiac dyssynchrony despite optimal pharmacological therapy. A CRT-D may be fitted to improve cardiac function and heart failure symptoms and also provide the ability to pace or shock the heart if necessary (either primary or secondary prevention of sudden cardiac death due to ventricular arrhythmia).

The three populations are not restricted by New York Heart Association (NYHA) classification, and patients with cardiomyopathy are not excluded from consideration in the appraisal.

The NICE scope did not indicate whether any subgroups of patients were of interest. No subgroups were predefined in the earlier guidance TA95 but subgroup analyses were reported in some included studies by left ventricular ejection fraction (LVEF), QRS duration, and history of heart failure requiring treatment. Subgroups that were thought to be of interest in TA120 and were therefore predefined were age, atrial fibrillation, NYHA class, degree of LVSD, degree of dyssynchrony, ischaemic and non-ischaemic heart failure. Relevant subgroups for this assessment may also include renal failure.

4.4 Definition of the interventions

Implantable cardioverter defibrillators (ICDs)

ICDs are battery powered electronic devices which are implanted into patients to continuously monitor cardiac rhythm. If an abnormal or life-threatening ventricular arrhythmia is detected the device will automatically deliver one of three treatments as appropriate: a series of low-voltage, fast rate electrical impulses to correct the heart rhythm (pacing); one or more electric shocks synchronised to the QRS complex to try and restore a normal heart rhythm (cardioversion), although in practice this is rarely utilised; or one or more non-synchronised electric shocks to try and restore normal heart rhythm (defibrillation). Sensing heart rhythm and delivery of electric impulses and/or shocks is achieved by one or more leads positioned inside the heart that connect to the pulse generator. The pulse generator is typically implanted under the skin in the upper chest near the left shoulder and almost all ICD leads are inserted into the heart through a vein (transvenous).[5] A subcutaneous ICD has been developed which avoids the use of transvenous leads, and this device senses the heartbeat without the need for a lead within the heart.[6] The potential advantages of this are avoidance of the complications that can be associated with transvenous lead insertion and removal of failed leads. A disadvantage of this device is that it cannot provide long-term pacing.[6]

Previous NICE guidance recommends ICDs for patients in the following categories:[7]

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

  • having survived a cardiac arrest due to either ventricular tachycardia or ventricular fibrillation

  • spontaneous sustained ventricular tachycardia causing syncope or significant haemodynamic compromise

  • sustained ventricular tachycardia without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF of less than 35%) (no worse than class III of the NYHA functional classification of heart failure).
- 'Primary prevention', that is, for patients who have:

  • a history of previous (more than 4 weeks) myocardial infarction and:

  either

  − left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the NYHA functional classification of heart failure), **and**

  − non-sustained ventricular tachycardia on Holter (24-hour electrocardiogram [ECG]) monitoring, **and**

− inducible ventricular tachycardia on electrophysiological testing

or

− left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the NYHA functional classification of heart failure) **and**

− QRS duration of equal to or more than 120 milliseconds (ms)

- a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia, or have undergone surgical repair of congenital heart disease.

TA95[7] does not cover the use of implantable defibrillators for non-ischaemic dilated cardiomyopathy.

The current technology assessment review will consider ICDs for the treatment of patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment.

Cardiac resynchronisation therapy – pacing device (CRT-P)

CRT-P is a type of pacemaker (also known as a biventricular pacemaker). Traditional pacemakers use one or two leads to sense and pace the right atrium and right ventricle or both, thereby stabilising the rate of contraction and ensuring contraction of the right ventricle occurs at the correct time interval after the contraction of the right atrium (AV synchrony).[8] For CRT-P a third lead is present which is used to pace the left ventricle via the coronary sinus. A CRT-P therefore not only provides AV synchrony but also aims to pace the ventricles so that after the atria contract both ventricles contract at the same time.[8]

Previous NICE guidance recommends CRT-P as a treatment option for people with heart failure who fulfil all the following criteria:[9]

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

The current technology assessment review will consider CRT for people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment.

Cardiac resynchronisation defibrillators (CRT-D)

A CRT-D combines the functions of a cardiac resynchronisation device with those of a pulse-generator which is able to pace or shock the heart as described above for ICDs.[8]

Previous NICE guidance recommends CRT-D for people who fulfil the criteria for implantation of a CRT-P device as stated in TA120[9] and who also separately fulfil the criteria for the use of an ICD device as recommended in TA95.[7]

Costs of the devices

The unit cost of CRT devices based on NHS Purchasing and Supply Agency estimates are £3,809 for a CRT-P device and £16,001 for a CRT-D device including leads, but these costs exclude VAT and the setting service costs.[9] Previous NICE guidance[10] also reported an average cost of approximately £18,000 per ICD device including the cost of overheads and implantation [inflated according to the Hospital and Community Health Services (HCHS) pay and price inflation indices[11]]. Previous cost-effectiveness analyses commissioned by NICE have shown that cost-effectiveness estimates for ICDs compared to optimal pharmacological therapy for ventricular arrhythmia varied between primary and secondary prevention scenarios and by other parameter values selected.[7] For CRT in comparison to optimal pharmacological therapy for heart failure, cost-effectiveness appears to be dependent on the time horizon of the analysis, improving with increasing time horizon (i.e. with greater extrapolation beyond the trial duration).[12] However when CRT-P devices are compared to CRT-D devices the most cost-effective option is CRT-P.[12;13]

4.5 Place of the intervention in the treatment pathway

ICD therapy can be regarded as a prophylactic intervention to reduce the risk of sudden arrhythmic death. Ventricular arrhythmias, particularly sustained ventricular tachycardia and ventricular fibrillation, are life-threatening events. Initial treatment will focus on restoring normal heart rhythm but thereafter the aim is to prevent any further episodes. Patients with sustained ventricular arrhythmias associated with haemodynamic compromise in the presence of left ventricular systolic dysfunction should be considered for ICD therapy after reversible factors are addressed. Optimal pharmacological therapy (as described in section 4.6 below) would be used as an adjunct or provided for those patients for whom an ICD would not be

appropriate (e.g. severely limited prognosis). Patients with LVSD and who have recently had a myocardial infarction or patients who have a cardiac condition that is associated with a high risk of sudden death should also be considered for ICD therapy in addition to optimal pharmacological therapy.

A patient presenting with the typical signs and symptoms of heart failure should receive specialist assessment including echocardiography.[14] If heart failure is diagnosed the goals of treatment are to reduce mortality and improve the health outcome of patients. In clinical practice, pharmacological agents are routinely used as the first-line therapy in managing heart failure (section 4.6).[15] However, as the severity of heart failure symptoms increases, patient symptoms may no longer be controlled by optimal pharmacological therapy. There are multiple syndromes associated with heart failure that could predispose patients to the need for further intervention**.** In patients with heart failure, the existence of a modifiable risk factor such as arrhythmias may constitute another rationale for the use of multiple interventions. The NICE pathway for chronic heart failure[14] indicates that when symptoms are not controlled by optimal pharmacological therapy, treatment with a CRT-P or a CRT-D can be considered for patients meeting the criteria already described in section 4.4. Comments received from a clinical expert indicate that CRT is increasingly being considered for people without symptoms with the aim of improving prognosis by modifying the natural history of heart failure. Another interventional procedure that may be considered for patients with severe refractory symptoms is cardiac transplant. For those awaiting a donor heart short-term circulatory support with a left ventricular assist device (LVAD) may be indicated.[16]

Variation in the provision of ICDs and CRTs is known to occur across England and Wales. A draft report produced using data from the Central Cardiac Audit Database compared implant rates in 2010 for ICDs and CRTs in each cardiac network (corrected for population demographics) with the accepted or notional target implant rates.[17] For ICDs the target rate recommended by NICE is 100 new implantations per million population. Only 4 of the 28 cardiac networks in England and Wales met or exceeded this target. The average rate of new implantations was 72/million with a range from the lowest rate of 38/million to the highest of 131/million. A similar picture emerged from the CRT device data which were reported in terms of both new and replacement CRT devices. Here the target rate of 130/million was met or exceeded by 11 of the 28 cardiac networks (average 117/million, range 66/million to 184/million). The report therefore shows that the chances of receiving one of these devices depends on where the patient lives although there is no evidence to suggest that demographically corrected implantation rates should differ between cardiac networks in different UK regions.

4.6 Relevant comparators

The comparators for this review vary according to the patient population. For people at increased risk of sudden cardiac death as a result of ventricular arrhythmias, the comparator is standard care, i.e. optimal pharmacological treatment without ICD. The most commonly used anti-arrhythmic drug in people who have already experienced ventricular arrhythmia is amiodarone, a class III drug according to the Vaughan Williams classification (classifies anti-arrhythmic drugs according to their effects on the electrical behaviour of myocardial cells).[18] Alternatives for people without left ventricular dysfunction or heart failure include flecainide, propafenone, and lidocaine.[18] For patients who have had ventricular tachycardia which has been restored to sinus rhythm and who remain at high risk of cardiac arrest (without left ventricular dysfunction or heart failure), beta-blockers, sotalol (in place of a standard beta-blocker), or amiodarone (in combination with a standard beta-blocker) can be used as stand-alone therapy when an ICD device is not appropriate.[18]

For people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony, the comparator is standard care (optimal pharmacological treatment without CRT). In addition, CRT-P and CRT-D will be compared with each other in line with the NICE scope. This is based on the 2010 Focused Update of ESC Guidelines[19] and the COMPANION trial,[20;21] which randomised people with heart failure to receive CRT-P or CRT-D after excluding people with an indication for an ICD. A NICE clinical guideline[15] recommends a variety of pharmacological treatments for patients with heart failure due to left ventricular systolic dysfunction and reduced left ventricular ejection fraction (Table 1). One clinical expert suggested that calcium channel blockers are best avoided in patients with depressed LV function, only amlodipine has been shown to be safe, and that there is little or no data supporting the use of inotropic agents in heart failure.

For people with both an increased risk of sudden cardiac death as a result of ventricular arrhythmias and heart failure as a result of LVSD and cardiac dyssynchrony, the comparators are ICD, CRT-P, or optimal pharmacological treatment alone. In the population with LVSD, optimal pharmaceutical treatment should include ACE inhibitor and beta-blocker. Other drugs in optimal pharmaceutical treatment may include an aldosterone inhibitor (spironolactone / eplerenone), and angiotensin II receptor blockers, especially in those not taking ACE inhibitors. Statin or aspirin would be used where ischemic heart disease was present. Ivabradine may also help in those with heart rates >70/min. Post MI patients without heart failure will require most of these drugs, specifically beta-blocker, ACE inhibitor, aspirin +/- clopidogrel, statin and possibly Omacor®.

Costs

Amiodarone costs £24.70 per patient year (200 mg per day). The estimated cost per patient year for ACE inhibitors ranges from £14.69 (for enalapril maleate at 20 mg per day) to £64.74 (for fosinopril sodium at 40 mg per day), with the most commonly used ACE inhibitors, ramipril and perindopril, estimated at approximately £21 per patient year (at 10 mg per day and 4 mg per day, respectively). The estimated cost per patient year for beta blockers, associated with ACE inhibitors, ranges from £14.17 (for the most commonly used beta blocker, bisoprolol fumurate, at 10 mg per day) to £69.68 (for nebivolol at 10 mg per day). All costs were estimated for non-proprietary formulations at maximum dosages listed in the current British National Formulary.[18] Costs of the devices being compared are presented in Section 4.4.

Table 1: Treatment for Chronic Heart Failure[15]

Treatment	**For heart failure due to left ventricular systolic dysfunction**	**For heart failure with preserved ejection fraction**
First line	Offer either an ACE inhibitor or a beta-blocker Consider an ARB (licenced for heart failure) as an alternative to an ACE inhibitor for patients with intolerable side effects Consider hydralazine in combination with nitrate for patients intolerant of ACE inhibitors and ARBs.	Manage comorbid conditions such as high blood pressure, ischaemic heart disease and diabetes mellitus in line with NICE guidance.
Second line	Consider the addition of an aldosterone antagonist or an ARB or hydralazine in combination with nitrate	
Drug treatment for all types of heart failure		
The following may be considered for	Diuretics Calcium channel blockers	

patients if appropriate	Anticoagulants Aspirin Inotropic agents Amiodarone

ACE = Angiotensin-converting enzyme, ARB = Angiotensin receptor blocker

4.7 Key factors to be addressed

As specified in the NICE scope, the following outcome measures are included in the decision problem:

- Mortality (including progressive heart failure mortality, non heart failure mortality, all cause mortality and sudden cardiac death)
- Adverse effects of treatment
- Health related quality of life (HRQoL)
- Symptoms and complications related to tachyarrhythmias and/or heart failure
- Heart failure hospitalisations
- Change in NYHA class
- Change in left ventricular ejection fraction

5. Report methods for synthesis of evidence of clinical effectiveness and cost-effectiveness

5.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (i) clinical-effectiveness studies of ICDs for arrhythmias and CRT for the treatment of heart failure; (ii) studies reporting on the cost-effectiveness of ICDs and CRT. Additional search strategies will also identify studies reporting resource use and costs, epidemiology and natural history of arrhythmias and heart failure.

The following electronic databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); Medline In-Process and Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); NIHR-Clinical Research Network Portfolio; Zetoc (Mimas); Clinical Trials.gov and Current

Controlled Trials. The draft clinical-effectiveness search strategy for Medline is shown in Appendix 9.1. This will be adapted for other databases.

Bibliographies of related papers will be assessed for relevant studies where possible. The manufacturers' submissions to NICE will be assessed for any additional studies that meet the inclusion criteria. Experts in the field will be contacted to identify additional published and unpublished evidence.

Literature searches will be carried out from database inception to the present for studies in the English language and will be limited to randomised controlled trials (RCTs) for the assessment of clinical effectiveness and to full economic evaluations for the assessment of cost effectiveness. Searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6) and may include a wider range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report to NICE.

5.2 Inclusion and exclusion criteria for systematic review of clinical effectiveness and cost-effectiveness

5.2.1 Population

- People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment
- People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment
- People with both conditions described above

5.2.2 Interventions

The interventions under consideration for each patient group are:

- For people at increased risk of sudden cardiac death:
    - ICDs in addition to optimal pharmacological treatment
- For people with heart failure:
    - CRT-P or CRT-D in addition to optimal pharmacological treatment
- For people with both conditions:
    - CRT-D in addition to optimal pharmacological treatment

5.2.3 Comparators

The comparators for each patient group are:

- For people at increased risk of sudden cardiac death:
    - Standard care (optimal pharmacological treatment without ICD)
- For people with heart failure:
    - CRT-P or CRT-D will be compared with each other
    - Standard care (optimal pharmacological treatment without CRT)
- For people with both conditions:
    - ICD
    - CRT-P
    - Standard care (optimal pharmacological treatment alone)

5.2.4 Outcomes

Studies must include one or more of the following outcome measures to be eligible for inclusion in this review:

- Mortality (including progressive heart failure mortality, non heart failure mortality, all cause mortality and sudden cardiac death)
- Adverse effects of treatment
- Health related quality of life
- Symptoms and complications related to tachyarrhythmias and/or heart failure
- Heart failure hospitalisations
- Change in NYHA class
- Change in left ventricular ejection fraction

5.2.5 Types of studies

- Only RCTs will be included for the assessment of clinical effectiveness.
- Studies published as abstracts or conference presentations from 2010 onwards will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- Systematic reviews of the clinical-effectiveness of ICDs and CRT will be used as a source of references.
- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations [cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses].
- Non-English language studies will be excluded.

5.3 Screening and data extraction process

5.3.1 Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed by two reviewers. Full papers of studies which appear potentially relevant will be requested for further assessment. These will be screened by two reviewers and a final decision regarding inclusion will be agreed. At each stage, any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

5.3.2 Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 9.2). Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

5.3.3 Quality assessment strategy

The quality of the clinical-effectiveness studies will be assessed according to criteria based on that devised by the Centre for Reviews and Dissemination (CRD, University of York)[22] and the Cochrane Collaboration.[23] Economic evaluations will be appraised using criteria based on those recommended by Drummond and colleagues,[24] and the checklist for assessing good practice in decision analytic modelling by Philips and colleagues[25] (Appendix 9.3). Published studies carried out from the UK NHS and Personal Social Services (PSS) perspective will be examined in more detail.

The quality of the individual studies will be assessed by one reviewer and checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted.

5.4 Methods of data analysis/synthesis of clinical-effectiveness data

Clinical-effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using specialised software such as Cochrane Review Manager 5 (RevMan). Where direct evidence is lacking, we will consider appropriate methods of indirect comparisons.[26] If considered appropriate by clinical experts and only where data allow, clinical- and cost-effectiveness will be assessed according to patient sub-groups. Possible subgroups that could be examined include age, degree of LVSD, QRS duration, ischaemic and non-ischaemic heart failure, effect of atrial fibrillation, NYHA class, and renal dysfunction.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Published and submitted economic evaluations

A systematic review of the literature will be conducted in order to identify published economic evaluations of the treatment of arrhythmias and heart failure, relevant to the UK NHS. The inclusion and exclusion criteria will be the same as for the clinical-effectiveness review, apart from study design as described in section 5.2. The quality assessment criteria are described in Section 5.3.3. The results of this review will include a narrative synthesis of the included economic evaluations alongside the data extraction tables.

Any economic evaluation included in sponsor submissions to NICE will be critically appraised using the same quality criteria as for published economic evaluations, but will be reported separately.

An additional systematic search of the literature will be conducted specifically for studies reporting HRQoL of adults with ventricular arrhythmias and/or heart failure. Useful HRQoL data may also be available in studies found in the clinical and cost-effectiveness reviews, and will be extracted if relevant. In the absence of evidence meeting our criteria, evidence from alternative sources may be used in the model.

6.2 Economic Modelling

Where appropriate, a decision analytic model will be built *de novo* for the current project, or developed through adaptation and update of one of the existing models from the previous NICE appraisal and published literature.[12;13] The perspective will be that of the NHS and PSS. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per QALY gained, as well as the cost per life year gained, if data permit. Both cost and outcomes will be discounted at 3.5%.

The appropriate model structure will be determined on the basis of the biological disease process, the main care pathways for patients in the UK NHS context and the disease states or events which are most important in determining patients' clinical outcomes, QoL and consumption of NHS or PSS resources. This will be informed by published clinical research evidence and expert opinion, as well as methods adopted in previously published economic evaluations and sponsor submissions to NICE. Parameter values will be derived from the best available evidence in the relevant research literature, including our own systematic review of clinical-effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or experts' clinical opinion. Searches for additional information regarding model

parameters, patient preferences and other topics will be conducted as required. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

The modelled population will be defined on the basis of both the published evidence about the characteristics of the UK population of people with ventricular arrhythmias, heart failure or both, and the populations for which good quality clinical-effectiveness is available. The base case results will be presented for adult populations with: (1) risk of sudden death due to ventricular arrhythmias; (2) heart failure (3) both risk of sudden death due to ventricular arrhythmias and heart failure.

The time horizon for our analysis will initially be governed by follow-up data available from included clinical trials. We will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

6.2.1 Methods for estimating quality of life

HRQoL data will be extracted from studies included in the clinical- and cost-effectiveness systematic reviews. Where available, the impact of treatment adverse effects on patients will also be incorporated. Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. In accordance with the NICE methodological guide for technology appraisals,[27] the utility values used in the model will be elicited where possible from the general population using a preference-based method. Where these are not available, utility estimates will be derived from alternative sources and the assumptions made will be explicitly stated.

6.2.2 Analysis of uncertainty

Assuming that the health gains from treatment can be expressed in QALYs, a cost-utility analysis will be conducted. The results of the analysis will be provided as incremental cost-effectiveness ratios (ICERs), i.e. the incremental cost per QALY gained.

Uncertainty in the model concerning the parameters and the structure used will be investigated through deterministic sensitivity analyses. If the data and modelling approach permit, joint parameter uncertainty will be explored by probabilistic sensitivity analysis, with

the results presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the assessment team no later than 13th July 2012. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with the NICE methodological guide for technology appraisals, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' material used in the assessment report will be highlighted in yellow and underlined.

8. Competing interests of authors

None.

9. Appendices

9.1. Draft search strategy

Database: Ovid MEDLINE(R) <1948 to October Week 1 2011>
Search Strategy:
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1 Defibrillators, Implantable/ (9177)
2 (implant* adj2 (defibrilat* or defibrillat*)).tw. (7443)
3 ICDs.tw. (1780)
4 (S-ICD or S-ICDS).mp. (12)
5 subcutaneous ICD*1.tw. (15)
6 implant* ICD*1.tw. (109)
7 (CRT or CRT-D or CRT-P).mp. (5504)
8 dual chamber ICD.tw. (99)
9 single chamber ICD.tw. (31)
10 resynch* therap*.tw. (2843)
11 ((heart or cardiac or myocardial or coronary) adj2 (resynch* or depolari* or repolari*)).tw. (4423)
12 (atriobiventricular adj10 pac*).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (13)
13 (atriobiventricular adj10 stimulat*).mp. (1)
14 BVP.tw. (171)

15 (biventricular adj10 pac*).mp. (1267)
16 (biventricular adj10 stimulat*).mp. (151)
17 (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*").tw. (10553)
18 or/1-17 (23746)
19 exp arrhythmia/ (151357)
20 Tachycardia, Ventricular/ or Arrhythmias, Cardiac/ or Tachycardia/ or Ventricular Fibrillation/ (81139)
21 Atrial Fibrillation/ (28211)
22 Heart Ventricles/bs, in [Blood Supply, Injuries] (883)
23 exp Ventricular Dysfunction, Left/ (18418)
24 exp cardiomyopathy, dilated/ (12085)
25 ventricula* remodel*.tw. (3058)
26 bundle-branch block/ (7157)
27 Heart Failure/ (75723)
28 exp heart failure, congestive/ (76964)
29 Death, Sudden, Cardiac/ (9588)
30 Heart Arrest/ (20243)
31 (ventricul* adj2 (tachycardia* or fibril* or arrhythmia*)).tw. (35081)
32 ((heart or cardiac or myocardial or coronary) adj2 (failur* or arrest* or sudden)).tw. (120348)
33 ((cardiac or ventricular or intraventricular) adj5 asynchron*).tw. (444)
34 ((cardiac or ventricular or intraventricular) adj5 dyssynchron*).tw. (887)
35 tachyarrhythmia*.tw. (6762)
36 "abnormal heart rhythm*".tw. (38)
37 ("unexpected death" or "sudden death").tw. (17259)
38 (cardiomyopathy or cardiomyopathies).tw. (39386)
39 Myocardial Infarction/ (130364)
40 "heart attack*".tw. (3279)
41 Long QT Syndrome/ (5342)
42 Syncope/ (8331)
43 (syncope adj2 (cardiogenic or heart or cardiac or myocardial)).tw. (533)
44 (atrial adj2 (fibril* or flutter*)).tw. (30953)
45 "sudden cardiac death".tw. (7320)
46 "unstable heart rhythm*".tw. (2)
47 "left ventricular systolic dysfunction".tw. (1671)
48 ((reduced or reduction or impair*) adj2 left ventricular ejection fraction).tw. (584)
49 LVSD.tw. (268)
50 ((heart or cardiac or myocardial) adj2 dysfunction*).tw. (10690)
51 exp cardiomyopathies/ (66092)
52 Brugada syndrome.tw. (1635)
53 arrhythmogenic right ventricular dysplasia.tw. (798)
54 ARVD.tw. (388)
55 (surg* adj5 "congenital heart disease").tw. (1347)
56 ((familial or genetic or inherited) adj "heart disease").tw. (54)
57 ("heart failure" or "cardiac failure" or "ventricula*1 failure").tw. (96985)
58 Heart Defects, Congenital/su [Surgery] (12506)
59 Heart Conduction System/ (26548)
60 exp Cardiac Pacing, Artificial/ (18389)
61 exp Pacemaker, Artificial/ (21321)
62 exp Heart-Assist Devices/ (7026)
63 or/19-62 (511661)
64 18 and 63 (17774)
65 Randomized Controlled Trials as Topic/ (77244)
66 randomized controlled trial.pt. (319496)

67 controlled clinical trial.pt. (83719)
68 Controlled Clinical Trial/ (83719)
69 random allocation/ (73314)
70 Double-Blind Method/ (113427)
71 Single-Blind Method/ (15643)
72 (random* adj2 allocat*).tw. (16712)
73 placebo*.tw. (133689)
74 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (110915)
75 Research Design/ (64888)
76 ((random* or control*) adj5 (trial* or stud*)).tw. (420466)
77 Clinical Trials as Topic/ (158838)
78 trial.ti. (96632)
79 random*.tw. (540954)
80 exp Placebos/ (30599)
81 Meta-Analysis/ (31210)
82 meta analysis.pt. (31210)
83 meta analys*.tw. (35262)
84 (systematic adj2 (review* or overview*)).tw. (30110)
85 Technology Assessment, Biomedical/ (7455)
86 (medline or embase or cochrane or pubmed).ab. (51691)
87 (systematic and (medline or embase or cochrane or pubmed)).ab. (11538)
88 (review and (medline or embase or cochrane or pubmed)).ab. (31605)
89 Evaluation Studies as Topic/ (119883)
90 exp Evaluation Studies/ (158960)
91 or/65-90 (1431934)
92 64 and 91 (3763)
93 (comment or editorial or letter).pt. (1094632)
94 92 not 93 (3556)
95 limit 94 to english language (3222)

9.2. Draft data extraction form (example)

Reviewer 1: **Date:**	**Reviewer 2:** **Date:**	**Version:**	
Pink text should be overwritten, delete guidance comments when finished. Avoid use of abbreviations			
Reference and design	**Intervention and Comparator**	**Participants**	**Outcome measures**
First author *et al.,* year{ref ID} Study acronym *Study design*: Country or countries *Number of centres*: *Funding*:	*Intervention*: *Comparator*: *Other interventions used*:	*Indication for treatment*: *Number of participants*: n = Intervention name, n= Comparator name, n= *Sample attrition/dropout*: *Inclusion criteria*: *Exclusion criteria*:	*Primary outcomes:* *Secondary outcomes:* *Method of assessing outcomes:* *Length of follow-up:*

Participant characteristics	**Intervention 1, n=**	**Intervention 2, n=**	**p value**
Age			
Gender			
Ethnicity			
Diagnosis			
Severity of disease e.g. NYHA classification			
Left-ventricular ejection fraction (LVEF)			
Heart rate			
Electrophysiology findings			
Current pharmacological therapy			
Cardiac history			
Previous treatment			
Comorbidities			
Comments:			
RESULTS			
Primary outcomes	**Intervention 1, n=**	**Intervention 2, n=**	**p Value**
Comments:			
Secondary outcomes	**Intervention 1, n=**	**Intervention 2, n=**	**p Value**
Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE			
Methodological comments • Allocation to treatment groups: • Blinding: • Comparability of treatment groups: • Method of data analysis: • Sample size/power calculation: • Attrition/drop-out:			
General comments • Generalisability: • Outcome measures: • Inter-centre variability: • Conflict of interests:			

Criteria for assessment of risk of bias in RCTs [22;23]

	Judgement[a]
Was the method used to generate random allocations adequate?	
Was the allocation adequately concealed?	
Were the participants and study personnel blind to treatment allocation?	
Were the outcome assessors blind to treatment allocation?	
Were attrition and exclusions reported, numbers in each group, and reasons for attrition/exclusions?	

Is there any evidence to suggest that the authors measured more outcomes than they reported?	
Any other sources of bias not addressed in other domains?	

[a] 'Low risk', 'high risk' or 'unclear risk' of bias

9.3. Critical appraisal checklist for economic evaluations

	Item	StudyID	Comments
1	Is there a clear statement of the decision problem?		
2	Is the comparator routinely used in UK NHS?		
3	Is the patient group in the study similar to those of interest in UK NHS?		
4	Is the health care system comparable to UK?		
5	Is the setting comparable to the UK?		
6	Is the perspective of the model clearly stated?		
7	Is the study type appropriate?		
8	Is the modelling methodology appropriate?		
9	Is the model structure described and does it reflect the disease process?		
10	Are assumptions about model structure listed and justified?		
11	Are the data inputs for the model described and justified?		
12	Is the effectiveness of the intervention established based on a systematic review?		
13	Are health benefits measured in QALYs?		
14	Are health benefits measured using a standardised and validated generic instrument?		
15	Are the resource costs described and justified?		
16	Have the costs and outcomes been discounted?		
17	Has uncertainty been assessed?		
18	Has the model been validated?		

Yes / No / ? (unclear)

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