NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

ENDURALIFE-powered CRT-D devices for the treatment of heart failure

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) assessment report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. For this topic, the EAC has also produced a technical review in response to questions raised by the Committee during selection and routing, which is appended to this report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: EAC technical report

1 The technology

The ENDURALIFE battery technology is designed to provide extended longevity in Boston Scientific cardiac resynchronisation therapy-defibrillator (CRT-D) devices compared to similar previous and current CRT-D devices. CRT-D devices are a treatment option for heart failure and arrhythmias. ENDURALIFE battery technology uses a lithium manganese dioxide (Li/MnO_2) battery chemistry, which is reported to be less susceptible to the variations in voltage and resistance associated with early battery depletion. CRT-D devices with ENDURALIFE battery technology are also designed to use less current than standard devices and are packaged in devices that are smaller than previous CRT-D devices. The ENDURALIFE battery technology is designed to be used only in Boston Scientific CRT-D and ICD devices.

2 Proposed use of the technology

2.1 Disease or condition

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 the circulation. It usually develops because the heart muscle is either too weak or too stiff. This condition can predispose to the development of life-threatening heart rhythm disturbances (arrhythmias) that originate from the main heart pumping chambers (ventricles) and put the patient at risk of sudden cardiac death. Heart failure can result from a number of other serious cardiac conditions, including coronary heart disease, valvular heart disease and high blood pressure (hypertension).

2.2 Patient group

The ENDURALIFE-powered CRT-D devices are intended for use in patients with heart failure who have left ventricular dysfunction, especially those who are at risk of sudden cardiac death. The specific heart failure population relevant to this evaluation is that described in NICE Technology Appraisal

314. Table 1 below summarises the specific patient groups indicated for this device.

Heart failure affects about 900,000 people in the UK. The condition develops in people of all ages, but is most common in older people – more than half of all people with heart failure are over the age of 75. The Hospital Episode Statistics (HES) database indicates that there were approximately 4,282 de novo CRT-Ds fitted in England in the 12 months to September 2015. Heart failure has a poor prognosis and an estimated 30–40% of patients will die within a year of diagnosis. Although prognosis is poor, there is evidence of a trend towards improvement in morbidity and mortality outcomes with newer treatments. The 6 month mortality rate decreased from 26% in 1995 to 14% in 2005.

2.3 Current management

The NICE guideline on chronic heart failure in adults covers the overall management. The NICE technology appraisal on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure recommends CRT-D as an adjunctive treatment option for people with heart failure on optimal medical therapy who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less as specified in table 1.

Table 1 Treatment options with CRT-D for people with heart failure who have left ventricular dysfunction with an LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB) (adapted from the NICE technology appraisal).

	NYHA class			
QRS interval	I	II	III	IV
<120 milliseconds				
120–149 milliseconds without LBBB				
120–149 milliseconds with LBBB		✓	✓	
≥150 milliseconds with or without LBBB	✓	✓	✓	

Key to abbreviations:
NYHA - The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure.
QRS - The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram.
LBBB - Left bundle branch block is a cardiac conduction abnormality seen on the electrocardiogram (ECG).

Implantation of an ENDURALIFE-powered device uses standard CRT-D insertion techniques (for further details see page 7-8 of EAC technical report and page 11 of assessment report). Expert advisers have stated that people with an implanted CRT-D are typically followed up by a physiologist in a technical device clinic and either a routine cardiology clinic or specialist heart failure clinic. Patients with a CRT-D implanted are usually required to attend a technical device clinic every 3 months unless remote tele-monitoring is being used. It is recommended that patients should have one face to face technical device review annually. Patients will additionally need to be seen in a cardiology clinic by a cardiologist; these clinics are dictated by clinical need/patient stability and are usually 6 monthly. Where possible the aim is to coincide the technical and cardiology clinics once a year. At each attendance, the patient's clinical status is noted and the device interrogated. The test includes: the pacing function; the defibrillation leads; lead impedance; the time spent pacing; and the incidence of arrhythmias. The rate of battery depletion and therefore the anticipated remaining life span of the device are also noted.

Remote device monitoring systems, which may reduce the need for technical device attendances, are available for all CRT-D devices, including those with ENDURALIFE battery technology. NICE has published a medtech innovation briefing on the LATITUDE NXT Patient Management System for monitoring cardiac devices at home.

2.4 Proposed management with new technology

The overall pathway of care for chronic heart failure patients would not be changed by the use of ENDURALIFE-powered CRT-D devices but the extended battery life could increase the time between replacements and therefore reduce the number of avoidable replacement procedures.

2.5 Equality issues

No equality issues were identified.

3 Sponsor's claimed benefits

The benefits to patients claimed by the sponsor are:

- Extended longevity devices could help improve patient experience by increasing the time between replacements (and hence reducing the number of avoidable replacement surgeries) a patient may be faced with in their lifetime.
- A reduction in replacement rates could be particularly beneficial for heart failure patients who are already very unwell and may have difficulty lying down for extended periods of time.
- A reduction in the number of replacement surgeries can reduce the risk of complications which is higher in replacement procedures than in de novo (initial) implant procedures. The increased risk of complications and infections can have a measurable impact on morbidity and mortality.

The benefits to the health system claimed by the sponsor are:

- A reduced chance of needing earlier replacement of the CRT-D device. The reduction of avoidable replacement procedures will lead to savings for the healthcare system - reduction in hospital admissions, bed days, and procurement costs. Preliminary estimates suggest it could represent £33 million over 6 years.
- More efficient use of resources as reduced replacement rates will allow more new patients to be implanted within the same resource constraints thus supporting the implementation of NICE's technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure and bridging the gap with recommended levels of CRT-D implants in the UK.

- A reduction in costs associated with replacement such as post-operative complications and infections.

4 Decision problem

Table 2 Summary of the decision problem

Population	Patients undergoing CRT-D device implantation for heart failure in line with NICE Technology Appraisal 314.
Intervention	CRT-D devices with ENDURALIFE battery technology.
Comparator(s)	CRT-D devices not incorporating ENDURALIFE battery technology (see also 'Cost analysis' below).
Outcomes	The outcome measures to consider include: • Device survival • Battery survival (or time to battery depletion) • CRT-D component failure • Number of invasive procedures including replacement surgeries • Incidence of complications due to replacement procedures for battery depletion and/or CRT-D component failure (as per definitions in the REPLACE registry) • Inpatient admissions; bed days (related to interventions) • Death • Patient satisfaction • Quality of life • Device-related adverse events
Cost analysis	Comparator(s): • CRT-D devices not incorporating ENDURALIFE battery technology. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Scenario and sensitivity analyses will be undertaken to address uncertainties in the model parameters including: - Warranty periods - Differences in performance between older and newer devices - Differences in battery performance between older and newer devices
Special considerations, including issues related to equality	Heart failure can affect people of all ages, but it is more common in older people – more than half of all people with heart failure are over the age of 75. Older people are protected groups under the Equality Act 2010.

In its submission, the company proposed the following variations to the intervention and comparator(s):

- Adverse events associated with replacement procedures based on any replacement procedure regardless of comparator due to lack of brand specific evidence.

The EAC judged the company's submission is relevant to the decision problem and considered clinical evidence on rates of complications based on replacement of a broader group of cardiac implantable electrical devices to be relevant to CRT-Ds.

The EAC's technical report, in response to uncertainties identified by the committee during selection and routing is at appendix D of this overview. It summarises factors that affect longevity of CRT-D devices, current standards for predicting longevity and Boston Scientific bench testing.

5 The evidence

5.1 Summary of evidence of clinical benefit

The company identified 15 published studies on battery survival and excluded 8 (no CRT-D devices included in the analysis (n=1), ENDURALIFE-powered devices <50% of the analysis (n=3), no quantitative findings (n=1) and proportion of ENDURALIFE-powered devices not reported (n=3)) leaving 7 observational case series on ENDURALIFE-powered CRT-D device longevity. Five full papers report on four individual studies (Alam et al, 2014 and Alam et al. 2016 report one study at different follow-up points) and two studies are conference abstracts. The EAC did not identify any further studies and agreed the 6 studies (reported in 7 papers) are relevant to the scope decision problem.

The company also presented 5 manufacturer-generated Product Performance Reports (PPRs) on device malfunction and survival probability. The EAC

accepted that PPRs showed that normal battery depletion, rather than CRT-D malfunction, is the main reason for CRT-D device replacement. It judged that the data in PPRs could not be used to compare longevity between ENDURALIFE-powered devices and other devices.

The company conducted a second literature search on adverse events associated with replacement procedures and presented 20 published studies (17 observational studies and 3 systematic reviews). The EAC excluded 14 of the 17 observational studies because of duplication of data between the studies. The EAC did not repeat the company's searches but judged that 1 further study (Kirkfedlt et al 2014) identified by clinical experts was relevant.

In total the EAC assessed:

- 6 observational studies on Enduralife battery longevity;
- 5 Product Performance Reports
- 6 studies on adverse events arising from cardiac device replacement

Battery longevity evidence

Alam et al. (2016) and Alam et al. (2014) are retrospective observational studies reporting on the same cohort, evaluating the time from device implantation to battery depletion at a single-centre in the USA. In the most recent publication 621 patients implanted with a CRT-D (Boston Scientific n=173 [n=122 ENDURALIFE-powered CRT-Ds], Medtronic n=391 and St Jude Medical n=57) between January 2008 to December 2010 were included. The last access to patients' medical records was December 2015; therefore the maximum possible follow up could be 8 years, and the mean follow-up was 3.4 years. Rates of CRT-D replacement due to battery depletion were: Boston Scientific 16%, St Jude Medical 53% and Medtronic 51%. When comparing battery depletion rates, Boston Scientific was longest compared to Medtronic (hazard ratio 0.15, 95% CI 0.10-0.22, $p<0.001$ and St Jude Medical (hazard ratio 0.28, 95% CI 0.16-0.48, $p<0.001$). The hazard ratios for battery depletion (adjusted for unbalanced electrical pacing parameters) were: Boston Scientific vs Medtronic 0.11 (95% CI 0.07,0.16), $p < 0.001$, Boston Scientific

vs St Jude Medical 0.25 (95% CI 0.13, 0.47), p < 0.001. Of the 67 patients alive 6 years post implantation battery survival was Boston Scientific 77%, St Jude Medical 44% and Medtronic 10%. 94 patients were lost to follow-up within a month of device implantation. The authors report the distribution of device manufacturer of patients lost to follow-up was equivalent to that of patients included in the analysis, therefore no adjusts were made to survival rates.

Ellis et al. (2016) is a retrospective USA multi-centre observational study designed to assess whether the battery capacity (in amperes) of a CRT-D device affects the period until the elective replacement indicator (ERI) is reached. A total of 1302 CRT-D devices (Boston Scientific n=322 [the company's submission states that 312/322 (97%) of Boston Scientific devices were ENDURALIFE-powered CRT-Ds], Medtronic n=794 and St Jude Medical n=186) were implanted between August 2008 and December 2010. The last follow up date was 31 December 2014 and mean follow-up was 3.0 ± 1.3 SD years. The proportion of devices reaching ERI over a mean follow-up of 3 years were: Boston Scientific 0.30% (ampere rating=2.0 Ah), Medtronic 13.5% (1.0 Ah) and St Jude Medical 3.8% (1.4 Ah). The odds ratio (OR) for reaching ERI with 1.0 Ah (Medtronic) device versus 1.4 Ah (St Jude Medical) or 2.0 Ah (Boston Scientific) was 9.73, p < 0.0001. Univariate predictors for ERI included 1.0 Ah device and LV pacing output >3V @ 1 ms (OR: 3.74, P < 0.001). Mortality rates in each manufacturer group were: Boston Scientific 28.0%, St Jude Medical 16.7% and Medtronic 21.8%. No CRT-D device failures were observed. High left ventricle lead impedance was protective of reaching ERI: OR (>1000 versus 500 Ohms) 0.38, 95% CI 0.20, 0.71, p = 0.0025.

Landolina et al. (2015) carried out a retrospective observational study in 9 Italian centres examining the rate of replacement for battery depletion and to identify reasons for early depletion. A total of 1726 CRT-Ds (Boston Scientific n=608 [291/608 = 47.9% ENDURALIFE-powered CRT-Ds], Biotronik n=49,

Sorin n=99, St Jude Medical n=172 and Medtronic n=798) were implanted from January 2008 to March 2010. The CRT-Ds were released onto the market from 2003 to 2010 and had different battery types; 708 were early-generation (released before 2007) and 1018 were recent-generation families (released since 2007). The median follow-up was 3.6 (IQR 1.5-4.4) years. Table 3 outlines some of the key results.

Table 3 Percentage of patients with reported events

	Battery depletion rate	CRT-D replacement rate (any cause)	Mortality rate
Boston Scientific	18%	22%	18%
Biotronik	20%	20%	12%
Medtronic	29%	34%	14%
Sorin	20%	22%	14%
St Jude Medical	20%	24%	20%

Among CRT-D devices classified as recent generation and excluding Sorin and Biotronik CRT-Ds (because there were fewer than 100 implants) the rates of devices still in service at five years were as follows: Boston Scientific 88%, St Jude Medical 75% and Medtronic 52%; log rank test p<0.01 for pairwise comparisons. Multivariate analysis factors associated with CRT-D replacement due to battery depletion are in table 4.

Table 4 Key factors associated with replacement for battery depletion in the overall population

	Hazard ratio	95% Confidence Interval	P-Value
Boston Scientific vs Medtronic	0.64	0.47-0.89	0.008
Recent generation device	0.57	0.45-0.72	<0.001
Battery chemistry			
Li/MnO2 vs Li/SVO	0.37	0.22-0.64	<0.001
Li/CFx-SVO vs Li/SVO	0.28	0.16-0.50	<0.001
High left ventricle lead output (pulse amplitude >2.5V, duration >0.5ms)	1.96	1.57-2.46	<0.001
Unipolar left ventricular lead	1.58	1.25-2.01	<0.001

Von Gunten et al. (2015) report findings from a 2 centre (Netherlands and Switzerland) retrospective observational study looking at device longevity. Only 26.3% of devices studies are CRT-Ds, however the results are presented separately for this subgroup (n = 1284 devices). The median follow up was 4.4 (IQR 2-7.3) years, longevity rates relate to devices that were still in use and the data split into devices implanted before and after 2006.

Table 5 Comparison of longevity of devices implanted in 2006 onwards

	Devices implanted in 2006 onwards	
	5-year longevity	6-year longevity
Boston Scientific	97.6%	97.6%
Biotronik	76.2%	44.9%
Medtronic	74.1%	46.3%
St Jude Medical	45.3%	26.5%
All manufacturers	66.3%	43.0%

Rates of CRT-D replacement were: Boston Scientific 30.9%; St Jude Medical 22.1%; Medtronic 36.3%; Biotronik 10.1%; Sorin 0% (only 4 Sorin CRT-Ds were studied). The rate of five year overall survival in patients with CRT-Ds (all manufacturers) was 72.8%. In the subgroup of 76 ENDURALIFE-powered COGNIS CRT-Ds there was 1 replacement representing 97.5% longevity at 4 years following implantation.

Lau et al. (2015) is a published abstract based on a conference poster presentation reporting the findings from a single centre UK hospital. The study compared battery longevity after 6 years of use of ENDURALIFE-powered CRT-Ds, Medtronic and St Jude Medical devices with smaller capacity batteries. At six years follow up, no Boston Scientific CRT-D devices required replacement due to battery depletion. St Jude Medical CRT-Ds began to reach ERI after 2.8 years and Medtronic CRT-Ds after 2.5 years. Pairwise comparisons showed a significant difference between Boston Scientific and St Jude Medical ($p<0.0018$) and between Boston Scientific and Medtronic ($p<0.0001$).

Williams and Stevenson (2014) is a published abstract from a conference poster presentation reporting on battery longevity of CRT-Ds implanted in patients at a USA hospital. The primary endpoint was device replacement for the battery reaching the ERI. A total of 90 CRT-Ds were implanted from July 2008 to July 2010 (final device follow up 31 October 2013): Boston Scientific n=53 [company's submission states 51/53 = 96.2% were ENDURALIFE-powered CRT-Ds], St Jude Medical n=10, and Medtronic n=28. At four year follow up the rates of ERI were: Boston Scientific 1.9%, St Jude Medical 10%, and Medtronic 50%. Multivariate analysis showed CRT-Ds reaching ERI had higher right ventricle lead output, left ventricle lead output and right ventricle pulse width (no values reported).

Manufacturer-generated Product Performance Reports (PPR) reporting on device malfunction and survival probability

Five PPRs were presented by the company in its submission, from 5 manufacturers of CRT-D devices. Production of PPRs is recommended by the US Heart Rhythm Society Task Force and has been taken up by all manufacturers of CRT-D devices. The aim of the PPR, which is based solely on data derived from explanted devices returned to the manufacturer, is to report device malfunctions in a standard format. The PPR is produced by the company and placed on its website.

Production of a PPR relies on efforts to track the key events in the life course of a CRT-D device, including implant date, specific events during the device's service life, and return of the device to the manufacturer for analysis following explantation. PPRs report survival probability in two ways (based on real, observed data): survival free from both malfunction and normal battery depletion; and survival free of malfunction alone leading to explantation in which cases of normal battery depletion are excluded from the analysis. Importantly in either case the definition of 'normal battery depletion' is a function of the manufacturer's predicted longevity. Predicted longevity is the anticipated device life based on developmental bench testing prior to

releasing the CRT-D to the market. It is important to note that this occurs under specific, controlled conditions which may not necessarily represent clinical use. The specific controlled conditions also differ by manufacturer.

The EAC sought clarification from the company about the methods used in the production of PPRs and concluded that PPRs have limitations preventing direct comparisons between different manufacturers' devices including:

- Boston Scientific PPRs are based on US implants due to a higher level of reporting in the US than internationally. Malfunctions of devices from other countries are recorded, but they are not used in the survival calculations in PPRs.

- Not all devices are returned to the manufacturer following explantation. The Boston Scientific PPR supplied in the company's submission reports that in the period 2008-2015, an estimated 58% to 68% of explanted CRT-Ds were returned to the company for analysis.

- PPR analysis assumes that a device is in-service unless otherwise indicated. A risk exists whereby explanted CRT-Ds that are not returned to the manufacturer may be classified as in use, instead of lost to follow-up. This would overestimate CRT-D longevity.

- The definition of normal battery depletion means that two devices from different manufacturers that reach a point of battery failure at the same length of follow-up may be classified as normal battery depletion or premature battery depletion (a malfunction). For this reason the survival probability based on combined malfunction plus normal battery depletion is the better outcome for comparison.

- PPRs report both malfunctions with CRT-D devices and also the leads (which are medical devices in their own right). These are reported separately. The company's submission includes only data on CRT-D devices, in line with the scope.

The EAC concluded that, in the context of this evaluation, the PPRs can only be relied upon to demonstrate that normal battery depletion, rather than CRT-D malfunction, is the most common reason that a CRT-D device needs to be replaced.

Adverse events associated with replacement procedures

Lewis et al. (2016) is a systematic review assessing the risks and benefits of ICD device replacement in which seventeen studies (n≥167,000 patients) were included. Complications reported included major complications (death and any complication that placed the patient at significant risk, required hospitalisation or surgical intervention) and minor complications (any other complication associated with significant symptoms or a decline in status not requiring surgical intervention such as incisional infection and pocket haematoma). The median rate for major complications was 4.05% (range: 0.55-7.37%) of which the most frequent was infection requiring antibiotic therapy and/or extraction (median rate 1.70% [range: 0-5.23%]). Other frequently reported major complications included:

- haematoma requiring evacuation (median 0.57%; range: 0-1.55%)
- reoperation for any other reason e.g. pocket erosion or device repositioning due to pain (median 1.56%; range: 0.07-3.24%)
- stroke (median 0.45%, range 0.01-0.82%).

The median rate for minor complications was 3.5% (range: 0.36-7.37%) with the most frequently reported being pocket haematoma (median 0.93%; range: 0.35-3.49%). Other frequently reported minor outcomes included, incisional infection (median 0.9%; range: 0.01-1.77%) and discomfort or pain at the site (median 0.44%; range: 0.39-0.45%).

Polyzos et al. (2015) conducted a systematic review and meta-analysis on risk factors associated with cardiac implantable electronic device (CIED) infection. Sixty studies were included with a total of 233,184 patients. The average reported device infection rate for included prospective studies was 1.6%

(n=21 studies), 1.0% for included case-control studies (n=9 studies) and 1.2% for included retrospective cohort studies (n=30 studies). The pooled odds ratio for the risk of infection associated with generator change (20 studies, 33,322 patients) was 1.74 (95% CI 1.22-2.19). Device replacement/revision was associated with a pooled odds ratio of 1.98 (95% CI [1.46-2.70]) for infection. The authors conclude that a “decision to replace a device should be made on a risk vs. benefit approach weighting the risk for death due to device failure, the rate of device failure, and the risk for procedure-related death”.

Zeitler et al. (2015) present a systematic review and meta-analysis of the complications associated with the replacement of cardiac implantable electronic device generators, following US Food & Drug Administration (FDA) recall. The review included seven studies (1,435 patients) with a primary end-point of major complications and mortality and reoperation/pocket revision as “other” end-points. Major complications were defined differently by the authors of the included studies, but overall it included any complication requiring reoperation (infection, bleeding/haematoma, system malfunction or pain) and any complication associated with device replacement. Device replacement following FDA recall was associated with a combined major complication rate of 2.60% (95% CI 0.9-4.8%). Five of the seven included studies reported mortality: 0.4% (95% CI [0.1-1.1%]). The rate of reoperation/pocket revision (5 studies) was 2.7% (95% CI [0.8-5.1%]). The authors conclude that generator replacement in response to a FDA recall has a similar rate of major complications as elective generator replacement. The authors also conclude that patient and device characteristics, patient preference and remaining battery life should all be considered when carrying out generator replacement, elective or otherwise.

The incidence of lead damage following CIED replacement procedures and its economic impact was investigated by Nichols et al. (2016). The authors reviewed health care claims data from the Truven Health Analytics MarketScan Commercial Research Database in the US. The study cohort

included 45,252 patients who underwent CIED replacement: 22,557 (50%) pacemaker generator replacements; 20,632 (46%) ICD device replacements; and 2,063 (5%) CRT-D device replacements. Lead damage was observed in 406 patients (0.90%) at a median of 107 days following devicer replacement. Lead damage incidence was 0.46% for patients with pacemakers, 1.27% for patients with ICDs and 1.94% for patients with CRT-Ds. In a Cox proportional hazards model, controlling for patient demographic and clinical characteristics, ICD replacement showed double (hazard ratio (HR) 2.00, 95% CI [1.57-2.55]) the risk of lead damage and CRT-D replacement showed >2.5 times (HR 2.58, 95% CI [1.73-3.83]) the risk of lead damage compared with pacemaker replacement. Out of the 406 patients with lead damage, 368 (91%) were in-patients with a median length of stay for lead damage of 3 days; this did not significantly differ based on the device type. The mean cost of lead damage management across all device types in the first year was $25,797. Average lead damage hospitalisation costs were significantly different across device types: $19,959 for pacemaker replacement; $24,885 for ICD replacement; and $46,229 for CRT-D replacement (p=0.048). The authors conclude that the higher rates of lead damage observed in ICD and CRT-D replacement are likely to be attributable to the greater number and complexity of leads in ICDs and CRT-Ds.

The risk of lead alerts following ICD generator replacement was investigated by Lovelock et al. (2014). This study utilised patients enrolled on the ALTITUDE project, an initiative to prospectively analyse data obtained from implanted Boston Scientific ICD and CRT devices through Boston Scientific's LATITUDE home monitoring system. A total of 60,219 patients were eligible for inclusion in this study, of which 7458 patients (12.4%) underwent ICD device replacement. A time dependent Cox proportional hazards model (adjusted for age, gender and ICD type) was used to evaluate potential associations between lead failure and device replacement. Lead performance in the 7458 patients undergoing device replacement was compared to leads of similar age (68 months) in patients who did not undergo device replacement.

Patients who underwent device replacement showed a 5-fold higher lead alert rate (HR 5.20, 95% CI [3.45-7.84]) when compared to those who did not; this was significantly different ($p<0.001$) even when covariates were adjusted for. Younger age and single lead ICD systems were also associated with an increase in lead alerts, hazard ratio 1.02, 95% CI [0.98-0.99] ($p<0.001$) and hazard ratio 2.49, 95% CI [1.96-3.17] ($p<0.001$) respectively. However, both age and system type was associated with lead alert to a lesser extent than device replacement. The authors suggest that surveillance is required following device replacement in addition to technique development and lead modifications to minimise the risk of lead damage during surgery. In another study Lovelock et al. (2012) reported that the rate of failure in Medtronic Fidelis leads was 20.8% following ICD device replacement and 2.5% in lead age-matched controls ($p<0.001$).

Kirkfeldt et al. (2014) was a retrospective multi-centre (14 hospitals) cohort study in Denmark which analysed complications occurring within 6 months on all cardiac implantable electronic devices implanted between May 2010 and April 2011. 5918 patients were included in the analysis; 74% (n=4355) received new implants, 19% (n=1136) device replacements and 7% (n=427) system upgrades or lead revisions. The complication rate was 5.9% following a device replacement. When complications are categorised, 3.5% of patients experienced a major complication within 6 months of having a device replacement.

EAC critical appraisal of the clinical evidence

The EAC concluded that the clinical evidence for the comparative longevity of CRT-Ds, based on four retrospective case series published in peer reviewed journal papers (plus two abstracted reports), is the best available evidence and reported no significant concerns about its quality and robustness. The EAC judged that the observational and retrospective nature of the analysis was a minor limitation and that the main weakness of the published data is that they appear to relate to devices no longer on the market due to the

incremental development of new models. A strength of the longevity studies is that they were conducted in as near to normal clinical practice as possible, and in countries that are similar to the UK in terms of population and care pathway.

In the Alam et al. studies (2014 and 2016) of, 122 of the 173 Boston Scientific devices studied were powered by the ENDURALIFE battery technology, the remainder being outside the scope of the evaluation. Based on the information reported, it is unclear if there was any selection, attrition and detection bias in the study. Ellis et al. (2016) report that the proportion of devices used in their study by manufacturer represents the market share distribution. No exclusions are reported and there were no obvious missing data. The paper reports differences in potential confounders across comparison groups. Landolina et al. (2015) do not report patient demographic and cardiac disease data, reporting differences across comparison groups in device parameters only. There were no substantial differences in follow up. The longevity study by von Gunten et al. (2015) includes a majority of data on implantable devices (74%) which are out of scope. The paper does not delineate baseline characteristics (demographic, cardiac morbidity, NYHA class, medical therapies) by analysis groups. Lau et al. (2015) is available as an abstract only and lacks details on patient factors, number of subjects per group and average follow-up. The study is most likely retrospective (not reported) and non-ERI events leading to removal of CRT-Ds from service were censored. Williams et al. 2014 is available as an abstract only and lacks values for some outcome data.

The five submitted Product Performance Reports depend upon explanted devices being returned to companies for analysis, or companies otherwise determining their status by active tracking. Production of Product Performance Reports is prone to differences in specifications across manufacturers and some reports have been shown to over-estimate CRT-D longevity compared to published clinical research studies. The clinical evidence on rates of

complications associated with replacement of CRT-Ds is based on replacement of a broader group of cardiac implantable electrical devices, but has acceptable applicability to replacement of CRT-Ds. The EAC concluded that the best available data on complications associated with replacement procedures is based on the Kirkfeldt et al. (2014) study.

Table 6 Characteristics of the key studies on ENDURALIFE battery longevity

Abbreviations used: ERI, OOS					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Alam et al. (2016)	Retrospective cohort, single centre (University of Pittsburgh Medical Center, USA). This is an update of the same cohort reported by Alam et al. 2014.	Patients implanted with CRT-D between 1 Jan 2008 and 31 Dec 2010: (last access to patient record 20 Dec 2015): Gender Male: 484/652 = 74% Female: 168/652 = 26% Age Mean 69 (SD 3) years Cardiac morbidity CHD 64% LVEV 29% (SD 12) Paced QRS width mean 155 ms (SD 29)	ENDURALIFE-powered CRT-Ds vs Medtronic and St Jude Medical CRT-Ds.	Primary outcomes Rate of device replacement for battery reaching ERI Time to battery depletion (HR) Secondary outcomes Time to battery depletion adjusted for unbalanced electrical pacing parameters between devices from different manufacturers	Losses to follow up since the publication of Alam 2014 seem to be patients with Medtronic CRT-D devices (n = 25). In the Boston Scientific group loss to follow up for 2014 (n = 32) versus 2016 (n = 31) may represent a minor error. Of 173 Boston Scientific devices studied, 122 were powered by the ENDURALIFE battery technology, so comparisons by manufacturer do not have complete applicability to the scope.
Alam et al. (2014)	Retrospective cohort, single centre (University of Pittsburgh Medical Center, USA) reported as full journal article.	Patients implanted with CRT-D between 1 Jan 2008 and 31 Dec 2010 (last access to patient record 15 Apr 2013): Gender Male: 484/652 = 74% Female: 168/652 = 26% Age Mean 69 (SD ±13) years	ENDURALIFE-powered CRT-Ds vs Medtronic and St Jude Medical CRT-Ds.	Primary outcomes Rate of device replacement for battery reaching ERI Battery survival at 4 years Secondary outcomes Predictors of battery depletion	. Of 173 Boston Scientific devices studied, 122 were powered by the ENDURALIFE battery technology, so comparisons by manufacturer do not have complete applicability to the scope.

Abbreviations used: ERI, OOS					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
		<u>Cardiac morbidity</u> CHD 64% LVEV 29 (SD ±12) % Paced QRS width mean 155 (SD ±29) ms			
Ellis et al. (2016)	Retrospective multicentre study (Vanderbilt Heart and Vascular Institute, USA) reported as full journal article.	1302 Patients (NYHA Class II-IV) implanted with CRT-D between 1 Aug 2008 and 31 Dec 2010 (last data entry 31 Dec 2014): <u>Gender</u> Male: 73% (n=950/1302) Female: 27% (n=352/1302) <u>Age</u> Mean 68.1 (SD ±11.8) years <u>Cardiac morbidity</u> Mean LVEF 25.1% (SD ±10.1%) Mean QRS duration 152.0 (SD ±25.6) ms Reason for implantation: Ischaemic cardiomyopathy 56.3% (n=731/1299)) Nonischaemic cardiomyopathy 41.9% (n=544/1299)	Device names not reported. Company reported the following: Comparison by Ah: - 2.0 Ah (Boston Scientific)=322 (312 of which ENDURALIFE-powered CRT-D, 97%)() - 1.0 Ah (Medtronic)=794 - 1.4 Ah (St. Jude)=186	<u>Primary outcomes</u> Proportion of batteries reaching ERI <u>Secondary outcomes</u> Predictors of ERI out of service (OOS).	. Authors report that the proportion of devices by manufacturer represents the market share distribution. No exclusions are reported.

Abbreviations used: ERI, OOS					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
		Type of implantation: De novo: n = 496/1302 (38.1%) Replacement: n = 480/1302 (36.9%) Revision: n = 52/1302 (4.0%) Upgrade: n = 274 (21.0%)			
Landolina et al. (2015)	Retrospective cohort study of nine centres (Italy).	1726 patients with heart failure implanted with CRT-D devices between Jan 2008 and Mar 2010 (data accessed March 2014). Implantation type: De novo: n = 1071 (62%) Replacement: n = 472 (27%) Upgrade: n = 183 (11%)	ENDURALIFE-powered CRT-Ds vs Biotronic, Medtronic, Sorin and St Jude Medical CRT-Ds.	Primary outcomes Rate of device replacement for battery reaching ERI Battery survival at 4 years Secondary outcomes Predictors of battery depletion	Of 608 patients in the Boston scientific group 291 had the Cognis CRT-D i.e. 48% were powered by the ENDURALIFE battery technology. Paper does not report patient demographic and cardiac disease data. Survival analysis (Kaplan-Meier & log-rank test): Patients were censored at the time of death (n = 274) or the last outpatient follow-up visit: 146 patients were censored due to receiving follow-up in other centres. In the analysis of the time to battery depletion, removals for other causes were not counted as events and patients were censored at the time of their

Abbreviations used: ERI, OOS					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
					occurrence. Although only 48% of BSC CRT-Ds were powered by the ENDURALIFE battery technology, the analysis of recent generation devices (marketed 2007 onwards) appears to include COGNIS devices i.e., 100% ENDURALIFE-powered CRT-Ds.
Lau et al. (2015)	Single centre (UK) case series reported as a conference abstract.	Patients with CRT-Ds implanted in 2008-9.	ENDURALIFE-powered CRT-Ds vs Medtronic and St Jude Medical CRT-Ds.	Primary outcomes Device survival until ERI Secondary outcomes None reported	Study available as abstract only: many details not reported, including patient factors, number of subjects per group and average follow-up. Study is most likely retrospective (not reported). Non ERI events leading to removal of CRT-Ds from service were censored.
von Gunten et al. (2015)	Retrospective cohort study (2 centres: Erasmus, Netherlands, Basel, Switzerland).	3436 Patients with heart failure of NYHA class I-IV fitted with 4881 ICDs (VVI, DDD, CRT-D) at two centres between March 1994 and January 2014. Data last accessed: 31 May	ENDURALIFE-powered CRT-Ds vs Biotronic, Intermedics, Medtronic and St Jude Medical CRT-Ds.	Primary outcomes Proportion of battery survival (longevity) at 4, 5, 6 years Battery survival at 4 years Secondary outcomes None reported	Full journal article. The paper reports on out-of scope implantable devices for the majority of participants (74%). The paper reports baseline characteristics (demographic, cardiac

Abbreviations used: ERI, OOS					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
		2014 (Erasmus), 30 June 2014 (Basel). N (CRT-D devices) = 1284/ = 26% N (BSC CRT-D devices) = 102/259 = 39%" <u>Gender</u> Male: 2721/3436 = 79% Age Mean 59 (SD±14) years <u>Cardiac morbidity</u> Mean LVEF 32 % (SD±13%) Mean QRS duration 127 (SD ±35) ms Ischaemic cardiomyopathy 74%			morbidity, NYHA class, medical therapies) for the entire cohort and not by analysis groups. Paper reports how many patients were censored due to competing risks (not reported by analysis group): 822 died 85 underwent heart transplant 189 moved to other hospitals 154 were lost to follow-up. A supplement to this paper reports longevity for 76 ENDURALIFE-powered COGNIS CRT-Ds at 4 years following implantation.
Williams et al. (2014)	Retrospective cohort at a single nonacademic community hospital (USA) reported as a conference abstract.	90 patients with CRT-Ds implanted between 1 July 2008 and 31 July 2010. <u>Age:</u> mean 72 (SD ±9) years <u>Cardiac morbidity:</u> Mean creatinine,1.3 (SD ±0.5) mg/dl Mean ejection fraction 0.25	Device names not reported. Company reported the following: Comparison by manufacturer: Boston Scientific=53	<u>Primary outcomes</u> Rate of device replacement for battery reaching ERI <u>Secondary outcomes</u> Multivariate Cox proportional hazard model to evaluate the covariates that can affect time to battery depletion	Study available in abstract only: full details not reported, including values for some outcome data.

Abbreviations used: ERI, OOS					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
		(SD ±0.08) %	(51 of which ENDURALIFE-powered CRT-D, 96%)(Medtronic=28 St. Jude=10		

5.2 Summary of economic evidence

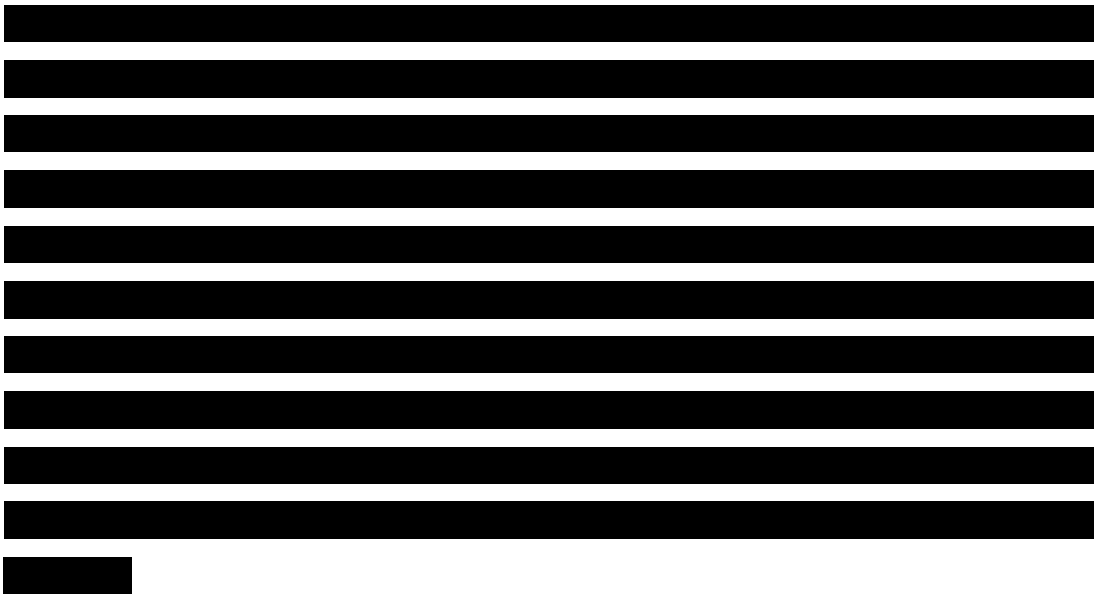
The company presented 7 economic studies comprising 6 published reports and 1 full paper supplied as academic in confidence. Three of the published studies were conference abstracts. The company did not rely on the presented economic studies for its model, although the structure of the de novo model is similar to that described in the Gadler et al manuscript.

The EAC considered the company's search strategy and inclusion/exclusion criteria reasonable but could be improved with access to more databases and a more thorough strategy. The EAC felt the population used by the company in its selection of economic evidence 'patients implanted with CRT-Ds' differs from the population specified in the scope which was 'Patients undergoing CRT-D device implantation for heart failure in line with NICE Technology Appraisal 314'. The company's population is broader and the EAC acknowledged that this probably reflects the lack of detail in the published evidence on the specific criteria used to define heart failure and CRT-D use in TA314.

The EAC excluded 3 papers included by the company as they were outside the scope. The Boriani et al. (2013) paper reports on a model comparing hypothesised CRT-D devices with 4 years and 7 years longevity over a 15 year time horizon. The devices were not specific named technologies and the longevities were not based on data, but were chosen to investigate the impact of longevity on costs. Therefore the paper is out of scope as it is not about the intervention (ENDURALIFE-powered CRT-Ds).The Biffi et al. (2011) paper was about ICD devices and included only 10 patients with CRT-Ds. It did not include devices from Boston Scientific and is therefore outside the scope. The Chung et al. (2015) abstract does not directly compare specific devices although it includes a device survival curve based on manufacturer data, but

looks at the costs for different patient groups of using devices with different longevity. Therefore the paper is outside the scope.

Gadler et al. (2016) is an accepted peer reviewed manuscript that is awaiting publication.



Landolina et al. (2016) is an economic analysis based on a subset of the data from Landolina et al. (2015) with a 6 year time horizon and two perspectives: a hospital perspective and the Italian healthcare system perspective. Boston Scientific provided funding for the economic analysis. Of 1,726 heart failure patients in Landolina 2015, 1,399 were included in the economic analysis. The analysis compares recent generation devices released from 2007-2010 with older generation devices released from 2003-2007 for 3 manufacturers (Boston Scientific, Medtronic and St Jude Medical) and for all manufacturers together. Weighted average prices of the devices were taken from tender information. The authors found that among recent generation CRT-Ds from different manufacturers the total cost per patient over 6 years ranged from €25,579 to €31,536 (£21,665 to £26,711 based on XE.com currency converter at €1 = £0.847 on 12 July 2016) with a maximum difference in cost of 40% for hospitals and 19% for the Italian healthcare system.

Priest et al. (2015) is a published abstract from a conference poster presentation comparing the costs for industry-standard and extended longevity devices from a Australian health system perspective over 15 years using real-world data for ICDs and CRT-Ds using the methods described by Boriani et al. 2013 (see Table C7 in company's submission for more details on this study). Patient survival following first implant was taken from published literature. Average longevity was taken from a recent NICE review (not specified, however the figures quoted are found in TA314), and Boston Scientific real-world longevity data from >100,000 ICDs followed on the Latitude remote device monitoring system. The study concluded that if all patients implanted switched from industry-standard devices to longer lasting batteries, this would decrease the average cost per patient by 19% and reduce the overall number of replacements by 70%. This would result in cumulative cost savings of more than $900 million over 15 years.

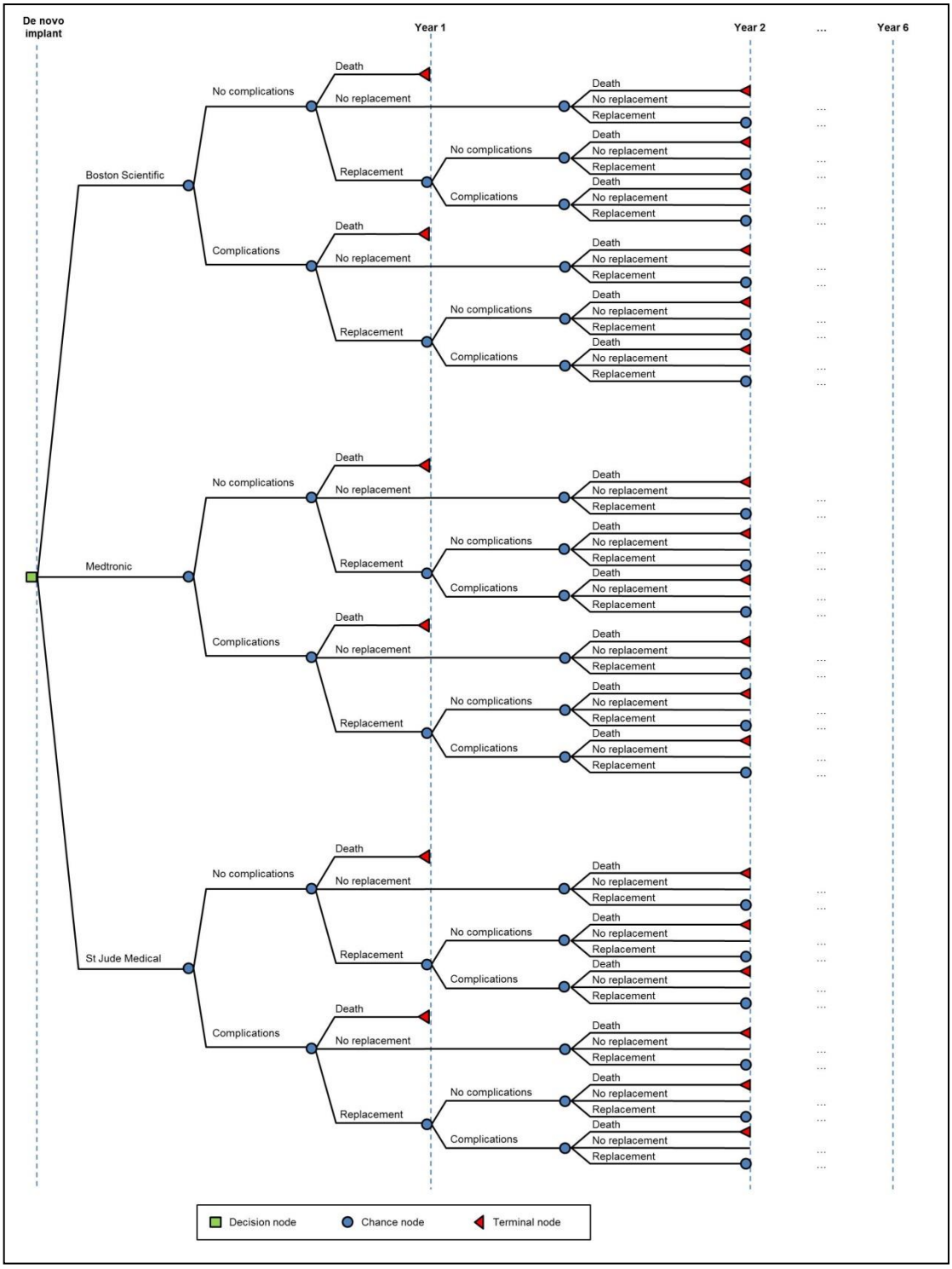
The paper by Duxbury et al. (2014) is a published abstract from a conference poster presentation reporting the economic impact of implanting ICDs and CRTs with extended longevity from a UK perspective. The methodology was similar to that of the Priest et al study (2015) in that it was based on the Boriani et al, 2013 study (see Table C7 in company's submission for more details on this study). It also used the average longevity described in the NICE technology appraisal on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure recommends CRT-D (7.1 years for ICD VR [single chamber ICD] and DR [dual chamber ICD),5.8 years for CRT-D], and Boston Scientific real-world longevity data from more than 100,000 ICDs followed in the LATITUDE Patient Management System (13.2 years for ICD-VR 11.5 years for ICDDR, and 9.2 years for CRT-D). The authors modelled the potential cumulative costs over 10 years for industry-standard and extended longevity battery life devices using real-world battery data for ICDs and CRT-Ds. The study concluded using devices with extended longevity rather than industry-standard battery longevity could result in potential cumulative savings of up to

£158 million over 10 years. This could mean over 9,400 new implants could be funded over a ten-year period, which would significantly increase the number of de novo implants within the NHS, without the need to increase capacity.

De novo analysis

The company noted that all of its selected economic studies were based outside the UK and did not carried out from a UK NHS perspective apart from the Duxbury et al (2014) abstract, which did not report on the cost impact for CRT-D devices separately. Therefore the company concluded that a new model was required. The company submitted a de novo cost analysis comparing ENDURALIFE-powered CRT-D devices (based on device models used in the Landolina et al. 2015 study) with Medtronic and St Jude Medical CRT-D devices (based on device models used in the Landolina et al. 2015 study). Costs were modelled from a UK NHS perspective and the population included was patients undergoing CRT-D device implantation for heart failure in line with NICE Technology Appraisal 314. The clinical data used in the model are taken from the Landolina et al. 2016 economic study which appears to be a sub-set of the same population as reported in Landolina et al. 2015. The model structure was a decision tree with a 6 year time horizon and an NHS perspective. For each make of implant there is a branch for complications or no complications, and for either of these cases there is a branch for death, replacement or no replacement at 1 year and at each subsequent year.

Figure 1 Company's de novo cost model



Key assumptions in the model are:

- The acquisition cost of the device is the same as the cost of the comparators.
- The warranty for the comparators is the same as for Boston Scientific devices.
- Patients attend outpatients 6 monthly for follow-up.
- Cost of warranty is not explicit in the model and therefore is assumed to be included in the cost of the device and equal for all devices.
- Data from published literature on devices implanted between 2008 and 2010 can be applied to the latest generation devices currently available from the same manufacturers.
- An estimated percentage improvement in projected battery survival was applied to Medtronic technologies to account for the expected improvement in the newer generation devices compared with those in the published literature.

Model parameters

Clinical data in the model is taken from the Landolina et al. (2016) for event-free battery survival and Yao et. al. (2007) for cumulative probability of patient survival. The incidence of complications is taken from Tang et. al. (2010) and the follow-up arrangements from NHS England 2013/14 NHS Standard Contract for Cardiology: Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronisation Therapy (CRT) (Adult). Table 7 summarises the clinical variables applied in the cost model.

Table 7 Clinical inputs applied to the base case cost model

Variable	Enduralife-powered CRT-Ds (Boston Scientific)	Medtronic CRT-Ds	St Jude Medical CRT-Ds
Cumulative probability of patient survival (Yao et al. 2007)			
Year 0	100%		
Year 1	95%		
Year 2	90%		
Year 3	85%		
Year 4	81%		
Year 5	77%		
Year 6	72%		

Cumulative probability of device survival (Landolina et al. 2016)			
Year 0	100%	100%	100%
Year 1	100%	100%	100%
Year 2	100%	99%	100%
Year 3	99%	92%	98%
Year 4	96%	78%	93%
Year 5	88%	50%	84%
Year 6	88%	30%	41%
Incidence of complications (initial implant and replacement procedures) (Tang et al. 2010)			
Infection	2.4%		
Complication requiring re-intervention[(a)]	8.5%		
Device-pocket problem requiring revision	0.5%		
Frequency of follow-up appointments per year (NHS England, 2013)			
Post-procedure follow-ups	1		
Ongoing routine follow-ups	2		

The model assumes follow up appointments at 6 month intervals with an additional post-procedure appointment. There is a trend towards tele-monitoring in the NHS as this releases cardiac physiologists time. There are additional items of equipment and software required to facilitate tele-monitoring. In addition, the interrogation of the device during tele-monitoring depletes the battery to some extent and therefore impacts upon the device longevity. This is discussed in more detail in the Technical Report (see appendix D). The model does not include tele-monitoring, but assumes all follow-up is conducted during face to face visits. The EAC considers the likely impact of including tele-monitoring on the per patient costing would be small, although it may have a significant impact on hospital services and patient experience.

Costs and resource use

The company used average selling prices for the UK NHS across all manufacturers derived from the economic modelling for NICE Technology Appraisal 314, and adjusted them for inflation using the 2015 Bank of England inflation rate of 0.9%. The company's rationale is that list prices are seldom

used when selling to hospitals and do not adequately reflect the actual cost to the NHS of these devices. This resulted in a mean cost for complete CRT-D system of £12,404 and £11,858 for a replacement implantable pulse generator only (excluding leads) for both ENDURALIFE-powered CRT-Ds and comparator CRT-Ds.

The company used procedure costs from the payment by results (PbR) tariff rather than NHS reference costs. The tariff is the price paid to the organisation for a procedure which may include adjustments to support particular policy goals, whereas NHS reference costs reflect the actual cost of the procedure averaged across the NHS. The EAC considered that NHS reference costs warranted exploration as a data source for the model, Table 8 represents the varying costs for PbR and NHS reference costs.

Table 8 Procedure costs used in the cost analysis

Model PbR code, description	Model PbR cost	NHS reference code, description	NHS reference cost
EA56Z Implantation of Cardiac Resynchronization Therapy Defibrillator (CRT-D)	£6201	EY01B Implantation of cardioverter defibrillator with cardiac resynchronisation therapy	£14,984
EA12Z Implantation of Cardioverter; Defibrillator only	£4700	EY10B Attention to cardiac pacemaker or cardioverter defibrillator	£2864
		EY09B Removal of cardiac pacemaker or cardioverter defibrillator	£3709

Table 9 shows the results of the model after replacing the PbR costs with NHS reference costs. The ENDURALIFE-powered CRT-Ds has increased from £22,322 (sponsor's base case) to £30,957.

Table 9 Results of model after substituting NHS reference costs for PbR tariff costs

ENDURALIFE-powered CRT-Ds	£30,957		
Medtronic CRT-Ds	£37,087	+ £6,131	+ 20%
St Jude Medical CRT-Ds	£35,429	+ £4,472	+ 14%

Table 10 shows the adverse event costs based on NICE TA314 cost model. A follow-up appointment cost £96 and was based on the Outpatient Attendance for Treatment Function 320: Cardiology (WF01A – Follow-up Attendance – Single Professional); 2016/17 National Tariff Payment System.

Table 10 List of adverse events and summary of costs included in the cost model

Adverse events	Value	Reference
Infection	£21,774	NICE TA314 economic modelling 2014 costs reported (£21,580) were inflated to 1 January 2016
Complication requiring re-intervention[(a)]	£6,152	NICE TA314 economic modelling**Error! Bookmark not defined.**; 2014 costs reported (£6,097) were inflated to 1 January 2016
Device-pocket problem requiring revision	£18,010	NICE TA314 economic modelling**;** 2014 costs reported (£17,849) were inflated to 1 January 2016

(a) Includes lead dislodgement and haematomas requiring intervention

The company's model assumed that all devices have the same cost and, because device cost is a key driver, the EAC saw this as a significant weakness. They stated that a new centralised procurement list is being developed to drive out variation and secure better prices from suppliers which includes CRT-D devices. This suggests that prices have been variable for these high cost devices, therefore the EAC considered the sensitivity analysis should explore differences in the price of the technology compared with the comparators to identify thresholds at which the model becomes cost neutral.

Results

Findings from the company's base case and sensitivity analyses are described on pages 73-78 of the assessment report. The results of the base case indicated that ENDURALIFE-powered CRT-D devices result in a cost saving of £6,836 per patient over a 6-year period when compared to Medtronic CRT-Ds and £4,986 per patient when compared to St Jude Medical CRT-Ds.

Additional work undertaken by the External Assessment Centre

The EAC obtained list prices for currently available CRT-D devices from the two manufacturers with which ENDURALIFE had been compared and ran the model with the supplied prices in place of the average selling price. The individual manufacturer list prices and subsequent analyses are reported on pages 79-87 of the assessment report. Changing the device cost in the model to the lowest and highest list price for each of the three manufacturers gives the result shown in Table 11.

[redacted]

[redacted]

[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The EAC accepted evidence in the company's submission that list prices do not reflect actual selling prices. However the assumption in the model that all of the device prices are the same (based on the generalised average selling price) is also unrealistic. The company explored varying the generic average selling price by +/- 20% for Medtronic CRT-Ds and for St Jude Medical CRT-Ds. Device cost was identified as a key driver of the model and so the EAC undertook threshold analysis. The threshold analysis investigated the effect of allowing a price difference between the devices and calculated the threshold at which the ENDURALIFE-powered devices become cost saving compared with the comparators. The results of this analysis are reported in Table 12.

Table 12 Device costs using threshold cost values

ENDURALIFE-powered CRT-Ds	£22,322		
Medtronic CRT-Ds	£22,042	-£281	-1%
St Jude Medical CRT-Ds	£22,058	-£264	-1%

If the cost of implanting the CRT-D and replacing the CRT-D is left as in the company's base case for ENDURALIFE-powered CRT-D devices, the technology becomes cost-incurring when the Medtronic implant cost is £7,546 and the St Jude implant cost is £8,546 with all other model inputs unchanged. Therefore accepting all else in the model, ENDURALIFE-powered CRT-Ds remain cost saving until they are £4,858 more expensive to purchase than Medtronic CRT-Ds and £3,858 more expensive to purchase than St Jude Medical CRT-Ds.

EAC critical appraisal of the economic evidence and model

The main weakness of the evidence is that it appears to relate to devices no longer on the market due to the rapid turnover of new models of the technology. For example the Medtronic models listed in the Landolina et al. 2016 study as 'recent generation' are the Consulta (withdrawn 2015), the

Maximo II (withdrawn 2016) and the Protecta (withdrawn 2016).

[redacted]

Gadler et al. was funded by Boston Scientific. The EAC felt the model used by Gadler is similar to the company's de novo model presented in the submission. The EAC conclude that Landolina et al. (2016) does not clearly specify which manufacturers supplied the least or most costly technologies over the 6 years. In the Priest et al. (2015) study the EAC consider the longevity data from the Latitude system may not be directly comparable with the longevity data reported in TA314, as the patient populations may be different. The EAC concluded that as the study is an abstract, there are insufficient descriptions of the methodology to enable a thorough critique and that the results should be treated with caution. The EAC had similar reservations regarding the Duxbury et al. (2014) study and concluded that the findings should also be treated with caution.

The 6 year time horizon of the model is a limitation and raises the question of whether a different result would be obtained if the time horizon encompassed the patient's lifetime. If patient life expectancy is 7 years, a device lasting 4 or 6 years is less relevant as patients would still require a replacement procedure, just at a different time point. Therefore the EAC conclude that the choice of a 6 year time horizon potentially exaggerates the cost saving of a slightly longer lasting device.

EAC conclusions

The EAC concluded that the company has submitted the best available evidence and there are no significant concerns about its quality and robustness. The EAC is concerned about the applicability of the evidence to inform decisions on device selection now as the available devices are different which was a weakness highlighted by the company.

The EAC state that the question of whether differences in longevity between ENDURALIFE-powered CRT-Ds and comparators lead to a reduction in replacement procedures depends on patient life expectancy.

The EAC identified an additional concern regarding the purchase price used in the model. Using the list prices from the manufacturers changes the result of the model from ENDURALIFE-powered CRT-Ds being cost saving to cost-incurring. Remaining uncertainties are the longevity of devices currently on the market, patient life expectancy, and the accuracy and comparability of manufacturer predicted device longevity from bench tests.

6 Ongoing research

The company identified one ongoing studies relevant to the decision problem, however estimated study completion date is 2021. NCT02091011 is a prospective, non-comparative single arm observational cohort study to assess rate and cause of device replacements for Boston Scientific ICDs and CRT-Ds at 5 years post-implantation. Enrolment completed in February 2016 with a total of 1600 patients recruited of which:

- US – 1347
- Canada – 106
- Korea – 47
- United Kingdom – 19
- Japan – 51
- Spain – 24
- Germany – 5
- Switzerland – 1

The EAC identified three additional ongoing studies, none of which are directly relevant to the decision problem. These are shown for information in Appendix 1 of the Assessment Report.

7 Issues for consideration by the Committee

Clinical evidence

The EAC feel some of the clinical evidence may be based on devices no longer on the market due to the rapid turnover of new models of the technology. For example some of the models listed in the Landolina et al. (2015) study as 'recent generation' have been withdrawn. As device longevity is related to other factors as well as battery technology, past performance is not necessarily indicative of future results.

The EAC considers that battery capacity is an important factor which may potentially determine CRT-D device longevity, but also that it cannot be considered in isolation and that other CRT-D factors are also important (see Technical Report in appendix D). It is likely that different manufacturers have all undertaken CRT-D development focussed on numerous CRT-D components such that devices marketed today may have better longevity than their predecessors studied in the included longevity studies.

Cost evidence

The EAC concluded that the 6 year time horizon of the model is a limitation and raises the question of whether a different result would be obtained if the time horizon encompassed the patients' entire lifetime. If most patients would require a device replacement during their lifetime, because even the longer lasting devices do not outlive most patients, then the question of when the replacement happens, before or after 6 years, is less critical. If the number of replacements in the patient's lifetime is the same, then the only difference in cost would arise from discounting for costs incurred in the future.

The purchase cost of the device is a key driver of the cost model. The company made an assumption that all devices had the same cost, using the average selling price data from TA314. The EAC concluded this was not appropriate as TA314 was a multiple technology appraisal and this evaluation is a single medical technology evaluation, where comparative price data from each device manufacturer is required to make a plausible cost case.

8 Authors

Liesl Millar, Technical Analyst

Paul Dimmock, Technical Analyst (Evaluations)

NICE Medical Technologies Evaluation Programme

August 2016

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Cleves, A., Carolan-Rees, G. and Evans et al., ENDURALIFE-powered CRT-D devices for the treatment of heart failure, August 2014

B Submissions from the following sponsors:

- Boston Scientific

C Related NICE guidance

- Acute heart failure: diagnosis and management NICE guideline CG187 (2014). Available from: www.nice.org.uk/guidance/cg187
- Chronic heart failure in adults: management NICE guideline CG108 (2010). Available from: www.nice.org.uk/guidance/cg108
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure NICE technology appraisal guidance 314 (2014). Available from: www.nice.org.uk/guidance/ta314
- Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults NICE interventional procedure guidance 482 (2014). Available from: www.nice.org.uk/guidance/ipg482
- Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure NICE interventional procedure guidance 463 (2013). Available from: www.nice.org.uk/guidance/ipg463
- Chronic heart failure in adults (2011) NICE quality standard 9
- Acute heart failure: diagnosis and management in adults (2015) NICE quality standard 103
- The AutoPulse non-invasive cardiac support pump for cardiopulmonary resuscitation (2015) NICE medtech innovation briefing 18.

- Services for people with chronic heart failure (2011) NICE commissioning guide 39
- Structural heart defects (2015) NICE pathway
- Acute heart failure (2015) NICE pathway
- Chronic heart failure (2015) NICE pathway
- Heart rhythm conditions (2014) NICE pathway

D References

Alam MB, Munir MB, Rattan R, Adelstein E, Jain S, Saba S. Battery longevity from cardiac resynchronization therapy defibrillators: differences between manufacturers and discrepancies with published product performance reports. Europace 2016 Mar 22.

Alam MB, Munir MB, Rattan R, Flanigan S, Adelstein E, Jain S, et al. Battery longevity in cardiac resynchronization therapy implantable cardioverter defibrillators. Europace 2014 Feb;16(2):246-51.

Biffi M, Ziacchi M, Bertini M et al. (2011) How to truly value implantable cardioverter-defibrillators technology: up-front cost or daily cost? Int J Technol Assess Health Care 27(3), 201-6

Biotronik. Cardiac Rhythm Management Product Performance Report January 2016. http://www biotronik com/wps/wcm/connect/en_de_web/biotronik/sub_top/healthcareprofessionals/product_performance/#jump 2016;Accessed from on 12 May 2016.

Boriani G, Braunschweig F, Deharo JC et al. (2013) Impact of extending device longevity on the long-term costs of implantable cardioverter-defibrillator therapy: a modelling study with a 15-year time horizon. Europace15(10),1453-62

Boston Scientific. Rhythm Management Product Performance Report Q1 2016. http://www bostonscientific com/en-US/pprc/product-performance-report html 2016;Accessed on 12 May 2016.

Chung ES, Gold MR, Curtis AB et al. (2015) Economic benefits of increasing battery longevity of cardiac resynchronization therapy defibrillator devices. Heart Rhythm 12(5), Suppl. 2015: S312 (Abstract).

Duxbury C, Canobbio M, Pinero F et al. (2014) The NHS cannot afford not to implant extended longevity devices to implement the nice guidance on ICD and CRT: modelling the budget impact over 10 years. Europace 16, Suppl.3:iii29

Ellis CR, Dickerman DI, Orton JM, Hassan S, Good ED, Okabe T, et al. Ampere Hour (Ah) as a Predictor of Cardiac Resynchronization Defibrillator Pulse Generator Battery Longevity; A Multi-Center Study. Pacing Clin Electrophysiol 2016 Feb 15.

Gadler F, Ding Y, Verin N et al. (2016) Economic impact of longer battery life of cardiac resynchronization therapy defibrillators (CRT-D) in Sweden. Clinicoecon Outcomes Res. 2016; submitted and under review accepted for publication.

Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J 2014 May;35(18):1186-94.

Landolina M, Curnis A, Morani G, Vado A, Ammendola E, D'onofrio A, et al. Longevity of implantable cardioverter-defibrillators for cardiac resynchronization therapy in current clinical practice: an analysis according to influencing factors, device generation, and manufacturer. Europace 2015 Aug;17(8):1251-8.

Landolina M, Morani G, Curnis A et al. (2016) The Economic Impact of Battery Longevity in implantable cardioverter-defibrillators for cardiac resynchronization therapy: the hospital and healthcare system perspectives. Europace; awaiting publication

Lau E, Wilson CM, Ashfield, McNair, Mceneaney, Roberts. Large capacity LiMnO2 batteries extended crtd longevity in clinical use compared to smaller capacity LiSVO batteries over 6 years. 2015.

Lewis KB, Stacey D, Carroll SL, Boland L, Sikora L, Birnie D. Estimating the Risks and Benefits of Implantable Cardioverter Defibrillator Generator Replacement: A Systematic Review. Pacing Clin Electrophysiol 2016 Jul;39(7):709-22.

Liva Nova. Cardiac Rhythm Management Product Performance Report November 2015. http://www livanova sorin com/medical-professionals/cardiac-rhythm-management/crmperformance 2016;Last accessed.

Lovelock JD, Cruz C, Hoskins MH, Jones P, El-Chami MF, Lloyd MS, et al. Generator replacement is associated with an increased rate of ICD lead alerts. Heart Rhythm 2014 Oct;11(10):1785-9.

Medtronic . Cardiac Rhythm Heart Failure Product Performance Report 2015 Second Edition - Issue 73. http://wwwp medtronic com/productperformance/past-reports html 2016;Last accessed: 12 May 2016.

National Institute of Health and Care Excellence. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure: NICE technology appraisal guidance [TA314]; June 2014. Accessed from https://www.nice.org.uk/guidance/TA314

Nichols CI, Vose JG, Mittal S. Incidence and Costs Related to Lead Damage Occurring Within the First Year After a Cardiac Implantable Electronic Device Replacement Procedure. J Am Heart Assoc 2016 Feb;5(2).

Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace 2015 May;17(5):767-77.

Priest VL, Haddrick N, Denman R et al. (2015) Economic value of improved ICD and CRT-D battery longevity in devices with a 1.7-2.0 ah capacity and li/mno2 chemistry in Australia. In: Saturday poster sessions of the 8th Asia Pacific Heart Rhythm Society Scientific Sessions, 2015, Melbourne, Australia. Page 69

St Jude Medical. Implantable Electronic Systems Product Performance Report 2016 1st Edition. https://professional sjm com/resources/product-performance/product-performance-reports/current 2016;Last accessed.

Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010 Dec 16;363(25):2385-95.

von Gunten S., Schaer BA, Yap SC, Szili-Torok T, Kuhne M, Sticherling C, et al. Longevity of implantable cardioverter defibrillators: a comparison among manufacturers and over time. Europace 2015 Nov 25.

Wild DM, Fisher JD, Kim SG, Ferrick KJ, Gross JN, Palma EC. Pacemakers and implantable cardioverter defibrillators: device longevity is more important than smaller size: the patient's viewpoint. Pacing Clin Electrophysiol 2004 Nov;27(11):1526-9.

Williams J. Contemporary cardiac resynchronization implantable cardioverter defibrillator battery longevities in a community hospital heart failure cohort. Journal of Cardiac Failure 2014;Conference(var.pagings):S56.

Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. Eur Heart J 2007 Jan;28(1):42-51.

Zeitler EP, Patel D, Hasselblad V, Sanders GD, Al-Khatib SM. Complications from prophylactic replacement of cardiac implantable electronic device generators in response to United States Food and Drug Administration recall:

A systematic review and meta-analysis. Heart Rhythm 2015 Jul;12(7):1558-64.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Roy Gardner
Consultant Cardiologist, British Society for Heart Failure

Dr Ernest Lau
Consultant Cardiologist, British Cardiovascular Society

Dr Chris Plummer
Consultant Cardiologist, British Cardiovascular Society

Dr David Jay Wright
Consultant Cardiologist, British Cardiovascular Society

Dr Zaheer Yousef
Consultant Cardiologist, British Cardiovascular Society

- Of the 5 expert advisers, 4 have had direct involvement with ENDURALIFE-powered CRT-Ds and 1 would like use this technology but it is not currently available to them. Two experts have been involved in research on this technology.
- All the experts felt that this technology is a significant modification of an existing technology with real potential for different outcomes and impact.
- The experts outlined the following benefits of an increased CRT-D longevity:
  - A reduction in the frequency of device replacement
  - Reduced risk of infection
  - Reduced inpatient stays
  - Reduce potential morbidity and mortality

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

- Arrhythmia Alliance
- Pumping Marvellous

- Reducing the number of battery changes can result in fewer surgical procedures. A reduction in surgical procedures decreases the chances of infection. The majority of heart failure patients are older people therefore reducing the number of interventions is beneficial as it avoids stress and possible complications. No disadvantages or equality issues relating to this technology were highlighted.

Appendix D: EAC technical report

See attached report ‘MT294 Enduralife Technical Assessment’.