

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

ENDURALIFE-powered CRT-D devices for treating heart failure

The National Institute for Health and Care Excellence (NICE) is producing guidance on using ENDURALIFE-powered CRT-D devices for the treatment of heart failure in the NHS in England. The Medical Technologies Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the public. This document should be read along with the evidence base (see sources of evidence considered by the committee).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Note that this document is not NICE's final guidance on ENDURALIFE-powered CRT-D devices for the treatment of heart failure. The recommendations in section 1 may change after consultation. After consultation the committee will meet again to consider the evidence, this document and comments from public consultation. After considering these comments, the committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the [Medical Technologies Evaluation Programme process guide](#) and [Medical Technologies Evaluation Programme methods guide](#).

Key dates:

- Closing time and date for comments: 17:00 23rd November 2016
- Second Medical Technologies Advisory Committee meeting: 16th December 2016

NICE medical technologies guidance addresses specific technologies notified to NICE by sponsors. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. If the case for adopting the technology is supported, then the technology has been found to offer advantages to patients and the NHS. The specific recommendations on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.

1 Provisional recommendations

- 1.1 The case for adopting ENDURALIFE-powered cardiac resynchronisation therapy-defibrillator (CRT-D) devices for treating heart failure is supported by the evidence. ENDURALIFE-powered CRT-Ds have a greater battery capacity and a longer battery life than non-ENDURALIFE powered CRT-Ds. Extended battery life is of clinical benefit and associated with fewer replacement procedures.
- 1.2 ENDURALIFE-powered CRT-Ds should be considered as a treatment option in people who are offered CRT-D devices in line with NICE TA314.
- 1.3 Cost modelling shows that the price and lifespan of the CRT-D have the greatest effect on overall treatment costs. Based on an average selling price of £12,404 across different devices, ENDURALIFE-powered CRT-Ds will save an estimated £2,120 to £5,627 per patient over 15 years as compared with other CRT-D devices through a reduction in the need for replacement procedures. This could save the NHS in England £6 million over 5 years.

2 The technology

Description of the technology

- 2.1 The ENDURALIFE battery technology (Boston Scientific) is designed to extend the battery life of Boston Scientific cardiac resynchronisation therapy-defibrillator (CRT-D) devices. CRT-Ds are a treatment option for heart failure and life-threatening ventricular arrhythmias. ENDURALIFE battery technology uses a lithium manganese dioxide (Li/MnO₂) battery chemistry, which is claimed to be less susceptible to the variations in voltage and resistance associated with early battery depletion. CRT-Ds with ENDURALIFE battery technology are also claimed to use less current and be smaller than other CRT-Ds.
- 2.2 ENDURALIFE battery technology was first incorporated into the COGNIS CRT-D device in February 2008. The ENDURALIFE brand was launched in 2015, but the technology has been in all Boston Scientific CRT-Ds since 2008; the CE marks for the AUTOGEN, DYNAGEN, INOGEN, ORIGEN, INCEPTA, ENERGEN, PUNCTUA and COGNIS CRT-Ds all include the ENDURALIFE battery technology. ENDURALIFE-powered CRT-Ds are CE-marked as class III medical devices.
- 2.3 According to the company's submission, ENDURALIFE-powered CRT-Ds cost £12,404. This cost was derived from the average selling prices used in the economic modelling for NICE technology appraisal guidance on [implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure](#). The cost was inflated using the 2015 Bank of England inflation rate of 0.9%.
- 2.4 The claimed benefits of ENDURALIFE-powered CRT-Ds in the case for adoption presented by the company are:

- Extended battery life for devices could help improve patient experience by increasing the time between replacements (meaning fewer overall replacement surgeries).
- A reduction in replacement rates could be particularly beneficial for patients with heart failure who are already very unwell and may have difficulty lying down for extended periods of time.
- A reduction in replacement rates will also reduce the risk of complications, which is higher in replacement procedures than in primary implants. The increased risk of complications and infections can have a measurable impact on morbidity and mortality.
- Fewer early replacement procedures will lead to savings for the healthcare system, such as a reduction in hospital admissions, bed days and procurement costs. Fewer replacement procedures also means a reduction in associated costs such as post-operative complications and infections. Preliminary estimates suggest it could represent £33 million over 6 years.
- Reduced replacement rates will allow more new patients to have implants within the same resource constraints, thus supporting the implementation of NICE's technology appraisal guidance on [implantable cardioverter defibrillators and cardiac resynchronisation therapy](#) and helping to meet the recommended levels of CRT-D implants in the UK.

Current management

- 2.5 NICE has issued guidance on the management of [chronic heart failure in adults](#). NICE technology appraisal guidance on [implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure](#) recommends CRT-Ds as an adjunctive treatment option for heart failure in people on optimal medical therapy who have left ventricular dysfunction with a left ventricular ejection fraction of 35% or less.

- 2.6 Implantation of an ENDURALIFE-powered device uses standard CRT-D insertion techniques. Expert advisers have stated that people with a CRT-D are typically followed-up by a physiologist in a technical device clinic and either a routine cardiology or specialist heart failure clinic. Patients with a CRT-D usually attend a technical device clinic every 3 months, unless remote telemonitoring is used. It is recommended that patients should have one face-to-face technical device review annually. Patients will also need to be seen by a cardiologist; these clinics are dictated by clinical need/patient stability but are usually 6-monthly. When 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. Tests include the pacing function, the defibrillation leads (including lead impedance), the time spent pacing and the incidence of arrhythmias. The rate of battery depletion, and therefore the anticipated lifespan of the device, is also noted.
- 2.7 Remote device monitoring systems, which may reduce the need for technical device attendances, are available for all CRT-Ds, 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](#).

3 Clinical evidence

Summary of clinical evidence

- 3.1 The key clinical outcomes for ENDURALIFE-powered cardiac resynchronisation therapy-defibrillator (CRT-D) devices in the decision problem were:
- device survival
 - battery survival (or time to battery depletion)
 - CRT-D component failure

- number of invasive procedures including replacement surgeries
- incidence of complications after replacement procedures for battery depletion or CRT-D component failure (as per definitions in the REPLACE registry)
- inpatient admissions and bed days (related to interventions)
- death
- patient satisfaction
- quality of life
- device-related adverse events.

3.2 The company did 2 searches for published literature on studies of device lifespan, the incidence of complications associated with device replacement, and outcomes relating to patient quality of life or satisfaction associated with device replacement. Its submission included: 6 case-series studies of CRT-D lifespan reported in 7 sources; 5 product performance reviews (PPRs, see section 3.9); and 20 studies (17 observational studies and 3 systematic reviews) that highlight the complications associated with implantable cardioverter defibrillators or CRT-D replacement. The external assessment centre (EAC) excluded 14 of the 17 observational studies because data from these studies were also used in the submitted systematic reviews. It judged that 1 further study on complications (Kirkfeldt et al. 2014), identified by clinical experts, was relevant. In total, the EAC assessed 6 observational studies on ENDURALIFE-powered CRT-D battery life (Alam et al. 2016, Ellis et al. 2016, Landolina et al. 2015, Von Gunten et al. 2015, Lau et al. 2015 and Williams and Stevenson 2014), 5 PPRs (Boston Scientific, Biotronik, Medtronic, Sorin and St Jude Medical) and 6 studies on adverse events arising from cardiac device replacement (Lewis et al. 2016, Polyzos et al. 2015, Zeitler et al. 2015, Nichols et al. 2016, Lovelock et al. 2014 and Kirkfeldt et al 2014).

Battery life

3.3 Alam et al. (2016) and Alam et al. (2014) are retrospective observational studies, both reporting on the same cohort, evaluating the time from device implantation to battery depletion. The most recent publication included 621 patients of which 122 had ENDURALIFE-powered CRT-Ds, 51 had a non-ENDURALIFE Boston Scientific device and 448 had a device from another company (Medtronic n=391, St Jude Medical n=57). The devices were implanted between January 2008 and December 2010 with a maximum possible follow-up of 8 years and mean follow-up was 3.4 years. Rates of CRT-D replacement because of battery depletion were 16% (Boston Scientific) compared with 51-53% for devices from other other companies. When comparing time to battery depletion, Boston Scientific devices lasted longer than either Medtronic (hazard ratio [HR] 0.15, 95% confidence interval [CI] 0.10 to 0.22, $p < 0.001$) or St Jude Medical devices (HR 0.28, 95% CI 0.16 to 0.48, $p < 0.001$). The hazard ratios for battery depletion (adjusted for unbalanced electrical pacing parameters) were:

- Boston Scientific compared with Medtronic: 0.11 (95% CI 0.07 to 0.16, $p < 0.001$)
- Boston Scientific compared with St Jude Medical: 0.25 (95% CI 0.13 to 0.47, $p < 0.001$).

Of the 67 patients still alive 6 years after implantation, battery survival rates were 77% (Boston Scientific), 44% (St Jude Medical) and 10% (Medtronic).

3.4 Ellis et al. (2016) is a retrospective observational study designed to assess how the battery capacity of a CRT-D affects the time until the elective replacement indicator (ERI) is reached. A total of 1,302 CRT-Ds (Boston Scientific n=322 (97.0% ENDURALIFE-powered CRT-Ds), Medtronic n=794 and St Jude Medical n=186) were

implanted between August 2008 and December 2010. Over a mean follow-up of 3 years, the proportions of devices reaching ERI were: 0.3% (Boston Scientific, battery capacity=2.0 Ah), 13.5% (Medtronic, 1.0 Ah) and 3.8% (St Jude Medical, 1.4 Ah). The odds ratio (OR) for reaching ERI with a Medtronic device (1.0 Ah) compared with a St Jude Medical (1.4 Ah) or Boston Scientific (2.0 Ah) device was 9.73 ($p < 0.0001$). Univariate predictors for ERI included 1.0 Ah device and an LV pacing output of over 3 V at 1 ms (OR: 3.74, $p < 0.001$). Mortality rates with each device were 28.0% (Boston Scientific), 16.7% (St Jude Medical) and 21.8% (Medtronic). No CRT-D failures were observed. High left ventricle lead impedance was protective of reaching ERI: OR (> 1000 versus 500 Ohms) 0.38, 95% CI 0.20 to 0.71, $p = 0.0025$.

- 3.5 Landolina et al. (2015) is a retrospective observational study examining the rate of replacement for battery depletion and to identify reasons for early depletion. A total of 1,726 CRT-Ds (Boston Scientific $n = 608$ [291 (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 commercially released between 2003 and 2010 and had different battery types; 708 were early-generation (released before 2007) and 1,018 were recent-generation families (since 2007). The median follow-up was 3.6 years. Among the recent-generation CRT-Ds (excluding those from Sorin and Biotronik, because there were fewer than 100 of these implants included in the study), rates of devices still working after 5 years were 88% (Boston Scientific), 75% (St Jude Medical) and 52% (Medtronic 52%). Table 1 shows multivariate analysis factors associated with CRT-D replacement because of battery depletion.

Table 1 Factors associated with CRT-D replacement because of battery depletion

	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/MnO ₂ vs Li/SVO	0.37	0.22–0.64	<0.001
Li/CF _x -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

3.6 Von Gunten et al. (2015) report findings from a retrospective observational study looking at device lifespan. Only 26.3% (n=1,284) of devices included in the study were CRT-Ds, but the results are presented separately for this subgroup. 39% of Boston Scientific CRT-Ds were powered by the ENDURALIFE battery technology. Median follow-up was 4.4 years. For devices implanted after 2006, the proportions of devices still working after 6 years were 97.6% (Boston Scientific), 26.5% (St Jude Medical), 46.3% (Medtronic) and 44.9% (Biotronik).

3.7 Lau et al. (2015) is a published abstract based on a conference poster presentation reporting the findings from a UK hospital. The study compared battery life after 6 years of use in Boston Scientific ENDURALIFE-powered CRT-Ds, and Medtronic and St Jude Medical CRT-Ds. At 6-year follow-up, none of the Boston Scientific devices needed replacement because of battery depletion. St Jude Medical CRT-Ds first 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).

3.8 Williams and Stevenson (2014) is a published abstract from a conference poster presentation reporting battery life of CRT-Ds. The primary end point was device replacement after reaching ERI. A total of 90 CRT-Ds were implanted from July 2008 to July 2010 (final device follow-up: October 2013): Boston Scientific n=53 (company's submission states that 51 [96.2%] were ENDURALIFE-powered), St Jude Medical n=10 and Medtronic n=28. At 4-year follow-up, the ERI rates were 1.9% (Boston Scientific), 10.0% (St Jude Medical) and 50.0% (Medtronic). Multivariate analysis showed that CRT-Ds reaching ERI had higher right ventricle lead output, left ventricle lead output and right ventricle pulse width (no values reported).

PPRs reporting on device malfunction and survival probability

3.9 Product performance reviews (PPRs) are based solely on data derived from devices that have been replaced and returned to the manufacturer. They aim to report device malfunctions in a standard format. 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 device removal (cases of normal battery depletion are excluded from the analysis). In both cases the definition of 'normal battery depletion' is a function of the manufacturer's predicted device lifespan (based on bench testing, which differs by manufacturer and may not accurately reflect clinical performance). The company presented 5 PPRs in its submission, from 5 manufacturers of CRT-Ds. The EAC accepted that the PPRs showed that normal battery depletion, rather than CRT-D malfunction, is the main reason for CRT-D replacement. However, it judged that data in the PPRs could not be used to compare the lifespan of ENDURALIFE-powered devices with that of other devices.

Adverse events associated with replacement procedures

- 3.10 Lewis et al. (2016) is a systematic review assessing the risks and benefits of replacing implantable cardioverter defibrillators, which included 17 studies (n≥167,000 patients). The median rate for major complications was 4.05% (range: 0.55% to 7.37%), of which the most frequent was infection needing antibiotic therapy and/or device removal (median rate 1.70% [range: 0 to 5.23%]). Other reported major complications included haematoma needing evacuation (median 0.57%; range: 0 to 1.55%), stroke (median 0.45%, range 0.01% to 0.82%) and reoperation for any other reason (such as pocket erosion or device repositioning because of pain; median 1.56%; range: 0.07% to 3.24%). The median rate for minor complications was 3.5% (range: 0.36% to 7.37%), with the most frequent being pocket haematoma (median 0.93%; range: 0.35% to 3.49%). Other reported minor outcomes include: incisional infection (median 0.9%; range: 0.01% to 1.77%) and discomfort or pain at the site (median 0.44%; range: 0.39% to 0.45%).
- 3.11 Polyzos et al. (2015) conducted a systematic review and meta-analysis on risk factors associated with cardiac implantable electronic device infection, including 60 studies with a total of 233,184 patients. The average reported device infection rates were 1.6 for prospective studies (n=21 studies), 1.0% for case-control studies (n=9 studies) and 1.2% for retrospective cohort studies (n=30 studies). The pooled OR for the risk of infection associated with generator change (20 studies; 33,322 patients) was 1.74 (95% CI 1.22 to 2.19). Device replacement was associated with a pooled OR of 1.98 (95% CI 1.46 to 2.70) for infection. The authors concluded that a 'decision to replace a device should be made on a risk/benefit approach weighting the risk for death because of device failure, the rate of device failure, and the risk for procedure-related death'.

- 3.12 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 7 studies (1,435 patients) with a primary end point of major complications and mortality; other end points included reoperation and pocket revision. Device replacement following FDA recall was associated with a combined major complication rate of 2.60% (95% CI 0.9% to 4.8%). Five of the 7 included studies reported mortality, which showed an overall mortality of 0.4% (95% CI 0.1% to 1.1%). The rate of reoperation/pocket revision (5 studies) was 2.7% (95% CI 0.8% to 5.1%). The authors conclude that generator replacement in response to an 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 replacing devices, elective or otherwise.
- 3.13 Nichols et al. (2016) investigated the incidence of lead damage following cardiac implantable electronic device replacement procedures and its economic impact. The study included 45,252 patients: 22,557 (50%) pacemaker generator replacements, 20,632 (46%) implantable cardioverter defibrillator 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 device replacement. Lead damage incidence was 1.94% for patients with CRT-Ds. In a Cox proportional hazards model, controlling for patient demographic and clinical characteristics, CRT-D replacement showed >2.5 times (HR 2.58, 95% CI 1.73 to 3.83) the risk of lead damage compared with pacemaker replacement. Of the 406 patients with lead damage, 368 (91%) were inpatients with a median length of stay for lead damage of 3 days; this did not significantly differ based on 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 implantable cardioverter defibrillator replacement; and \$46,229 for CRT-D replacement ($p=0.048$). The authors conclude that the higher rates of lead damage observed in implantable cardioverter defibrillator and CRT-D replacement are likely to be attributable to the greater number of and complexity of leads in these procedures.

- 3.14 Lovelock et al. (2014) investigated the risk of lead alerts after replacing implantable cardioverter defibrillators. This study utilised patients enrolled on the ALTITUDE project, an initiative to prospectively analyse data obtained from implanted Boston Scientific devices through its LATITUDE home monitoring system. A total of 60,219 patients were eligible for inclusion in the study, of which 7,458 patients (12.4%) had implantable cardioverter defibrillator replacement. A time-dependent Cox proportional hazards model (adjusted for age, gender and device type) was used to evaluate potential associations between lead failure and device replacement. Lead performance in the 7,458 patients having device replacement was compared with leads of similar age (68 months) in patients who did not have device replacement. Patients who had device replacement showed a 5-times higher lead alert rate (HR 5.20, 95% CI 3.45 to 7.84) compared with those who did not; this was significantly different even when covariates were adjusted for ($p<0.001$). Younger age and single-lead implantable cardioverter defibrillators were also associated with an increase in lead alerts: HR 1.02, 95% CI 0.98 to 0.99, $p<0.001$; HR 2.49, 95% CI 1.96 to 3.17, $p<0.001$ respectively. However, both age and system type were associated with lead alerts to a lesser degree than device replacement. The authors suggest that surveillance is needed after 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 device replacement and 2.5% in lead age-matched controls ($p < 0.001$).

- 3.15 Kirkfeldt et al. (2014) was a retrospective multicentre (14 hospitals) cohort study in Denmark which analysed complications occurring within 6 months of cardiac electronic devices implanted between May 2010 and April 2011. The analysis included 5,918 patients: 74% ($n=4,355$) had new implants, 19% ($n=1,136$) had device replacements and 7% ($n=427$) had system upgrades or lead revisions. The complication rate was 5.9% following a device replacement. When complications were categorised, 3.5% of patients experienced a major complication within 6 months of a device replacement.

EAC's critique of the clinical evidence

- 3.16 The EAC felt that the longevity studies were conducted under similar conditions to normal clinical practice but were retrospective and it was not possible to determine the rationale for choice of CRT-D. The published studies demonstrate that ENDURALIFE-powered CRT-Ds implanted since 2008 have greater longevity than comparator CRT-Ds. However some of the CRT-Ds studied in the longevity studies, particularly for comparator devices, may no longer be marketed.
- 3.17 The EAC accepted the company's submission of evidence on the rate of complications following replacement procedures for CRT-D. The EAC acknowledged that the PPRs submitted by the company demonstrated that, for the majority of implanted CRT-Ds, it is normal battery depletion that leads to CRT-D replacement, and not device malfunctions.

Committee considerations

- 3.18 The committee concluded that the evidence showed that ENDURALIFE-powered CRT-Ds have a greater battery capacity and longer battery life compared with other available CRT-Ds. It was noted that some of the studies the committee had considered included CRT-Ds no longer in use. However, clinical experts advised that the company's claims relating to battery life and the ENDURALIFE technology have been borne out in the published literature and their own clinical practice.
- 3.19 The committee heard from clinical experts that battery depletion depends on a number of factors including the needs of the patient, lead technology, battery design and the algorithms used in the CRT-D. They also advised that, notwithstanding other developments in CRT-D and battery technology, one of the central factors in lifespan is related to the charge a battery is capable of carrying; this has changed little across all manufacturers in the recent past. Compared with others, Boston Scientific ENDURALIFE batteries have one of the largest charge ratings.
- 3.20 The committee was advised that replacement procedures are associated with a risk of serious complications and that complications are more common in replacements than in primary implants. Infection can have major consequences in terms of patient morbidity and resource use, including the need for hospital admission that may last days or weeks. The committee heard from a patient expert that replacement procedures have a detrimental impact on patients' quality of life. Clinical experts also advised that replacement procedures are regarded by their patients as a significant life event.
- 3.21 The committee heard from the clinical experts that predicting a patient's individual life expectancy after device implantation is difficult. Nonetheless, experts advised that given the prognostic

benefit of CRT-D implantation in patients with heart failure, the choice of a CRT-D device with a greater lifespan is logical.

- 3.22 The committee was advised that CRT-Ds differ in size and shape between manufacturers and that Boston Scientific devices are slightly thinner than others. Experts stated that the shape of the CRT-D is sometimes more important than the size, and that the choice of device needs to be personalised to the patient's individual needs. This usually involves shared decision-making between the patient and the clinician.

4 NHS considerations

System impact

- 4.1 The company claimed that a reduction in avoidable replacement procedures will lead to fewer hospital admissions, bed days and procurement costs. Fewer replacement procedures could result in more efficient use of resources, because it would allow more primary (that is, non-replacement) implants within the same resource constraints. The company also claimed that using ENDURALIFE-powered cardiac resynchronisation therapy-defibrillator (CRT-D) devices could lead to cost savings through a reduction in associated costs such as post-operative complications and infections.

Committee considerations

- 4.2 The committee was advised by clinical experts that although replacements are done for a variety of reasons, including lead failures, 80% to 90% of CRT-D replacements are because of battery depletion.
- 4.3 The committee heard from experts that the cost of replacing a CRT-D is between £10,000 and 15,000, not including the cost of additional leads.

- 4.4 The committee was advised that telemonitoring and remote monitoring affect battery drain across all manufacturers' devices.
- 4.5 The committee heard from experts that, despite battery life being an important patient benefit, it is standard practice for a single centre to use CRT-Ds from more than one manufacturer. The rationale is to spread the risk of undue pressure on clinical services in the face of possible future device-related technical failure necessitating recall and replacement.

5 Cost considerations

Cost evidence

- 5.1 The company identified 7 studies that incorporated a cost-effectiveness analysis. It did not rely on these economic studies for its model, but the structure of the de novo model is similar to that described in Gadler et al. (unpublished). The external assessment centre (EAC) judged the company's search strategy and inclusion/exclusion criteria reasonable, but noted that it could be improved with access to more databases and a more thorough strategy. The EAC considered that the population used by the company in its selection of economic evidence – 'patients implanted with cardiac resynchronisation therapy-defibrillators (CRT-Ds)' – differed from the population specified in the scope. 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 from the NICE technology appraisal guidance on [implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure](#).
- 5.2 The EAC excluded 3 studies included by the company because they were outside the scope. Boriani et al. (2013) report on a model comparing hypothesised CRT-Ds with 4-year and 7-year lifespans

over a 15-year time horizon. The devices were not specifically named technologies and the lifespans were not based on data, but were chosen specifically to investigate how battery life affects costs. Biffi et al. (2011) focused on implantable cardioverter defibrillators and included only 10 patients with CRT-Ds. It did not include devices from Boston Scientific. 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 using devices with different lifespans.

- 5.3 The accepted for publication Gadler et al. manuscript describes an economic model and was submitted as academic in confidence.
- 5.4 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 compared 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.
- 5.5 Priest et al. (2015) is a published abstract from a conference poster presentation comparing the costs for industry-standard and extended-lifespan devices from an Australian health system

perspective over 15 years, using real-world data for implantable cardioverter defibrillators and CRT-Ds (using the methods described by Boriani et al. 2013). Patient survival following first implant was taken from published literature. Average battery life was taken from a recent NICE review (not specified, but the figures quoted are found in NICE's technology appraisal guidance on [implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure](#)), and Boston Scientific real-world battery life data from more than 100,000 for implantable cardioverter defibrillators using the LATITUDE NXT remote monitoring system. The study concluded that if all patients switched from industry-standard devices to extended-lifespan batteries, the average cost per patient would fall by 19% and overall number of replacements would fall by 70%. This would result in cumulative cost savings of more than \$900 million over 15 years.

- 5.6 The paper by Duxbury et al. (2014) is a published abstract from a conference poster presentation reporting the economic impact of implanting cardiac devices with extended lifespans from a UK perspective. The methodology was similar to that of the Priest et al, study (2015), in that it was based on Boriani et al. (2013). It also used the average lifespans described in the NICE technology appraisal and Boston Scientific real-world battery life data using the LATITUDE NXT remote monitoring system. The authors modelled the potential cumulative costs over 10 years for industry-standard and extended-lifespan devices using real-world battery data for implantable cardioverter defibrillators and CRT-Ds. The study concluded that using devices with extended battery life could result in cumulative savings of up to £158 million over 10 years.

EAC's critique of the cost evidence

- 5.7 The EAC identified the main weakness of the published economic evidence was it relates to devices no longer marketed, due to the rapid turnover of new models of the technology. The study by

Gadler et al. was funded by Boston Scientific, so may be subject to bias. The EAC considered the longevity data from the Latitude system used in Priest et al. (2015) may not be directly comparable with that reported in TA314, as the patient populations may be different. The EAC concluded that as the Priest et al. (2015) and Duxbury et al. (2014) studies are only available as abstracts, the results should be treated with caution.

Cost model

- 5.8 The company presented a de novo economic model adapted from Gadler et al. (2016) estimating mean cost savings per patient. The model is a decision tree with a 6-year time horizon and an NHS perspective. It compares Boston Scientific ENDURALIFE-powered CRT-Ds with Medtronic and St Jude Medical CRT-Ds. For each device there are branches for procedural complications or no complications, with further branches for death, replacement or no replacement at 1 year and at each subsequent year. Clinical data in the model are taken from the Landolina et al. (2016) study on 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 and cardiac resynchronisation therapy (adult). The model assumes follow-up appointments at 6-month intervals with an additional post-procedure appointment.
- 5.9 The company's scenario analyses included exploring differences in device survival and device cost to identify thresholds at which the model becomes cost neutral. The price was varied by $\pm 20\%$ for each device separately using a one-way sensitivity analysis. The analyses showed that the cost model is highly sensitive to changes in both device survival and device cost. Higher device survival resulted in a marked decrease in relative costs. The one-way

sensitivity analysis of device cost showed that ENDURALIFE-powered CRT-Ds remained cost saving.

- 5.10 The company's base case showed that ENDURALIFE-powered CRT-Ds cost £22,322 per patient over a 6-year period compared with £27,309 and £29,158 per patient for St Jude Medical and Medtronic CRT-Ds respectively. The company therefore estimated that using ENDURALIFE-powered CRT-Ds would save between £4,987 and 6,836 per patient over 6 years. Cost savings come mainly from fewer replacement procedures.

Additional work by the external assessment centre

- 5.11 The EAC re-ran the company's base case and univariate sensitivity analyses and conducted additional analyses using its preferred estimates. The EAC also did a threshold analysis using the average selling price for ENDURALIFE-powered CRT-Ds and allowing the cost of the comparator devices to fall to the point at which each becomes cost neutral. The main changes to the company's model were:
- Changes to the list prices of ENDURALIFE-powered CRT-Ds and both comparators.
 - Using warranty data from the comparator manufacturers instead of that from Boston Scientific.
 - Using NHS reference costs instead of Payment-by-Results tariff costs.
 - Changes to the sensitivity analysis for complication rates (infection), based on the results of a large Danish cohort study (Kirkfeldt et al. 2014). This changed the infection rate from 2.4% to 0.6%.
 - Using patient survival data from the National Institute for Cardiovascular Outcomes Research instead of from Yao et al. (2007).

- 5.12 The results of the EAC analysis suggested that changing the device cost in the model to the lowest and highest list price for each of the 3 manufacturers results in ENDURALIFE-powered CRT-Ds becoming more costly than those from Medtronic, but remaining cost saving compared with those from St Jude Medical.
- 5.13 The threshold analysis investigated the effect of allowing a price difference between the devices, and calculated the threshold at which ENDURALIFE-powered CRT-Ds become cost incurring compared with the comparators. The results showed that, using the same cost of implanting and replacing the CRT-D as used in the company's base case, ENDURALIFE-powered CRT-Ds become cost incurring when 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, with all other model inputs unchanged.
- 5.14 Using NHS reference costs instead of the Payment-by-Results tariff increased the cost of ENDURALIFE-powered CRT-Ds from £22,322 in the company's base case to £30,957. ENDURALIFE-powered CRT-Ds remain cost saving compared with the comparators but to a lesser extent than in the company's base case.
- 5.15 Substituting the actual warranty information supplied by the manufacturers into the model showed that ENDURALIFE-powered CRT-Ds remained cost saving.
- 5.16 Changing the rate of infection for new implants from 2.4% to 0.6% had little effect on the costs.
- 5.17 Using data from the National Institute for Cardiovascular Outcomes Research (NICOR) instead of from Yao et al. (2007), ENDURALIFE-powered CRT-Ds remained cost saving when using the company's base-case device cost. At the lowest and highest list

prices, ENDURALIFE-powered CRT-Ds become more costly than those from Medtronic, but remain cost saving compared with those from St Jude Medical.

- 5.18 The EAC concluded that the main driver of the cost model is device price.
- 5.19 The committee considered that the 6-year time horizon made the cost case uncertain. The EAC was therefore asked to carry out further analyses extrapolating the data available over a patient's lifetime (sections 5.20 to 5.25).
- 5.20 Following expert advice, the EAC contacted NICOR, which holds a registry of patients who have had CRT-Ds in NHS hospitals, including data on overall survival.
- 5.21 NICOR provided unpublished data in confidence which showed patient survival by age group after primary implantation of a CRT-D.
- 5.22 The EAC extrapolated CRT-D lifespan to 15 years using a survival profile for comparator devices: this took an average distribution based on Medtronic and St Jude Medical CRT-D lifespans reported in Landolina et al. (2015), and then applied the average distribution to the ENDURALIFE-powered CRT-Ds from the point at which the ENDURALIFE-powered CRT-Ds begin to reach the elective replacement indicator (ERI), at 5 years following implantation.
- 5.23 The EAC extrapolated patient survival to 15 years using NICOR data for patients aged 50 to 84 years at primary implantation.
- 5.24 Using the average selling price in the company's base case and the extrapolated data outlined above, the results showed that ENDURALIFE-powered CRT-Ds cost £28,234 per patient over 15 years compared with £30,354 and £33,861 per patient for St Jude Medical and Medtronic CRT-Ds respectively. The EAC therefore

estimated that using ENDURALIFE-powered CRT-Ds would save between £2,120 and £5,627 per patient over 15 years.

- 5.25 A threshold analysis investigated the effect of allowing a price difference between the devices, and calculated the threshold at which ENDURALIFE-powered CRT-Ds become cost incurring compared with the comparators. The results showed that, using the same cost of implanting and replacing the CRT-D as used in the company's base case, ENDURALIFE-powered CRT-Ds become cost incurring when they are £3,304 more expensive to purchase than Medtronic CRT-Ds and £1,404 more expensive to purchase than St Jude Medical CRT-Ds.

EAC's critique of the cost model

- 5.26 The EAC considered the 6 year time horizon of the model as a limitation and a time horizon over the patient's lifetime may be more appropriate. They concluded that the choice of a 6 year time horizon could overestimate the potential cost saving of a slightly longer lasting device.

Committee considerations

- 5.27 The committee was advised that device costs were accurately reflected in the company's base case which used average selling prices and that prices are similar between manufacturers. List prices are not a true reflection of what the NHS pays for CRT-Ds.
- 5.28 The committee concluded that it would be difficult to ascertain actual NHS prices for ENDURALIFE-powered and comparator CRT-Ds. The EAC was asked to carry out a differential cost threshold analysis, to overcome some of these uncertainties.
- 5.29 The committee accepted the EAC's revisions to the company cost-modelling provided the most plausible estimates of the cost consequences of adopting ENDURALIFE-powered CRT-Ds.

6 Conclusions

- 6.1 The committee concluded that there is good evidence to support the clinical benefit of extended battery life and the associated reduction in cardiac resynchronisation therapy-defibrillator (CRT-D) replacement procedures. ENDURALIFE-powered CRT-Ds have been shown to have a greater battery capacity and longer battery life compared with other CRT-Ds.
- 6.2 The committee concluded that, although some of the published evidence relates to devices not currently in use, the recent advances in CRT-D technology are unlikely to negate the benefits of ENDURALIFE-powered battery performance on device lifespan compared with other devices.
- 6.3 The committee concluded that, on the basis of cost modelling analysis, the use of ENDURALIFE-powered CRT-D devices is likely to be cost saving in patients with heart failure as a result of a reduction in the need for replacement procedures.

Peter Groves
Chairman, Medical Technologies Advisory Committee
October 2016

7 Sources of evidence considered by the Committee

The external assessment centre report for this assessment was prepared by Cedar:

- Cleves A, Carolan-Rees, G, Dale M et al. ENDURALIFE-powered CRT-D devices for the treatment of heart failure (July 2016)

Submissions from the following company:

- Boston Scientific

The following individuals gave their expert personal view on ENDURALIFE-powered CRT-Ds by providing their expert comments on the draft scope and assessment report.

- Dr Chris Plummer, Consultant Cardiologist, British Cardiovascular Society
- Dr David Jay Wright, Lead Clinician for Heart Failure, British Cardiovascular Society

The following individuals gave their expert personal view on ENDURALIFE-powered CRT-Ds in writing by completing a patient questionnaire or expert adviser questionnaire provided to the committee.

- 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, Lead Clinician for Heart Failure, British Cardiovascular Society
- Dr Zaheer Yousef, Consultant Cardiologist, British Cardiovascular Society