External Assessment Centre report

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the Company's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

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

Produced by: Cedar

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Declared interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

If there are none, please state 'none'.

Acknowledgements

The EAC is grateful for the contributions of two expert clinical advisors:

Dr Jay Wright, Consultant Cardiologist, Liverpool Heart and Chest Hospital

Dr Chris Plummer, Consultant Cardiologist, The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Related documents

NICE commissioned Cedar to produce a Technical Assessment of the ENDURALIFE-powered CRT-Ds. This describes the technical factors that can affect battery longevity in CRT-Ds, discusses methods of presenting longevity, documents technical specifications of currently marketed devices and describes battery life testing completed by Boston Scientific.

Contents

1 Summary

Scope of the Company's submission

The Company's submission is relevant to the decision problem defined in the Scope.

Summary of clinical evidence submitted by the Company

The Company has provided evidence on the longevity of ENDURALIFE-powered CRT-Ds compared to comparator CRT-Ds in the form of six case series studies (referred to by first author: Alam, Ellis, Landolina, Lau, von Gunten, Williams) [1-7], four of which are published in full (Alam, Ellis, Landolina, von Gunten) [1-4;6] and two of which are available as abstracts [5;7]. One of the case series studies is reported in two papers, the second with longer follow-up [1;2]. All analyses are retrospective. The studies show that for devices implanted during the time interval c2008-c2010, ENDURALIFE-powered CRT-Ds have better longevity than their contemporarily implanted comparator CRT-Ds. In the Landolina study [4] the number of CRT-Ds still in service at five years following implantation were 88% for Boston Scientific, 75% for St Jude Medical and 52% for Medtronic. In the company's economic model CRT-D longevity data were used as inputs based on a subsequent, accepted-for-publication economic analysis by the same group of authors and based broadly on the same patient series (Landolina 2016, unpublished). For ENDURALIFE-powered CRT-Ds implanted during this period, the advantage in longevity represents a longer interval until a replacement procedure is required. The Company's submission includes Product Performance Reports (PPRs) which, for this evaluation serve only to demonstrate that it is normal battery depletion, rather than CRT-D malfunction, that is the main reason that a CRT-D device needs to be replaced. The evidence on rates of complications associated with CRT-D replacement procedures is fairly clear: a large, Danish cohort study reports that replacement procedures carry a 5.9% risk of any complication and a 3.5% risk of major complications.

Summary critique of clinical evidence submitted by the Company

The 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 acceptably robust. Three of the studies include over 1000 participants. A minor limitation is that analyses are observational and retrospective. 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 best available data on complications associated with replacement procedures is based on a large Danish cohort study.

Summary of economic evidence submitted by the Company

The Company submitted 7 economic studies and a de novo model. They relied on the de novo model to support their claimed benefits and used the published and unpublished economic studies to demonstrate consistency with the published literature.

Summary critique of economic evidence submitted by the Company

The EAC excluded 3 of the economic studies as outside of the scope.

In the model the company relied upon the same average selling price data from TA314 for each of the technologies, which is not fit for purpose in this single medical technology evaluation where we need to see price data from each manufacturer for their technologies.

The company relied in the model on applying Boston Scientific's warranty arrangements to the comparator technologies.

There was an attempt by the company to update longevity data to reflect improvements in longevity of current technologies, but this assumed that the device survival profile across each manufacturer was unchanged since 2008-10.

The 6 year time horizon of the model was chosen because of available follow-up in the clinical studies. A better time horizon would be based on patient life expectancy to demonstrate whether differences in device replacement rates are significant in relation to life expectancy.

External Assessment Centre commentary on the robustness of evidence submitted by the Company

The clinical evidence submitted by the company is acceptably robust and reflects the performance of ENDURALIFE-powered CRT-Ds implanted in the period c2008-c2010, showing their superiority at that time in terms of CRT-D longevity. The nature of undertaking empirical research in real life clinical settings is that lengthy follow-up is needed to see useful longevity data: only recently have the relevant peer reviewed results been published, and these form the basis of the Company's submission. A procurement professional today would observe that newer and different CRT-D models are supplied today, compared to the models in the published studies described above. The EAC considers that there have likely been numerous innovations across different manufacturers since the time when these studies were initiated. Such innovations are unlikely to be limited to the battery alone, but to other components of the device (e.g. capacitor, microprocessor) and to how it interacts with the heart. These are discussed in detail in the technical assessment. The EAC considers that the empirical evidence in the Company's submission is robust, but it is uncertain whether it has direct applicability to CRT-Ds marketed today. Whether differences in longevity between ENDURALIFE-powered CRT-Ds and comparators lead to a reduction in replacement procedures depends on patient life expectancy.

Summary of any additional work carried out by the External Assessment Centre

The EAC searched for and did not identify any further studies of head-to-head comparisons of CRT-D longevity across manufacturers. Based on expert clinical advice, the EAC has included a Danish cohort study providing data on rates of complications associated with replacement procedures.

The EAC obtained list prices for the technology and the comparators and re-ran the model using these inputs for device cost. The EAC also did a threshold analysis using the average selling price for the ENDURALIFE powered CRT-Ds and allowing the comparator purchase cost to fall to the point at which each becomes cost neutral.

The EAC obtained warranty data from the comparator manufacturers and substituted this into the formulae in the model.

The EAC substituted NHS reference costs where the company had used PbR tariff costs in the model.

Based on information from clinical advisers the EAC modified the sensitivity analysis for complication rates (infection) based on the results of a large Danish cohort study.

2 Background

2.1 Overview and critique of Company's description of clinical context

The Company presents a thorough description of the clinical context for ENDURALIFE powered CRT-D devices. The population is described as per the Scope i.e. people with heart failure and a left ventricular ejection fraction (LVEF) <35%, classified according to New York Heart Association (NYHA) functional classification system, presence/absence of left bundle branch block (LBBB) and QRS interval observed on electrocardiogram (ECG). Higher NYHA class (range I-IV) represents more life-limiting heart failure. The Company's description of clinical context makes reference to, and is consistent with NICE TA314 and NICE CG108.

CRT-Ds are one type of a number of implantable devices that may be indicated in the NICE care pathway. All implantable devices are selected after medical therapies have been attempted.

The Company cites evidence suggesting that the number of patients receiving de novo CRT-Ds is growing and also the number of patients undergoing replacement CRT-D procedures.

The Company's submission is appropriate and relevant to the decision problem under consideration. The Company's main claimed benefit is that ENDURALIFE-powered CRT-D devices would require less frequent replacement than comparator CRT-D devices. For patients this would bring a benefit through less frequent invasive surgery and its risk of complications. A system benefit would result from releasing a quantity of cardiac catheterisation clinic time for other procedures. There are no other significant changes in care pathway arising through the use of ENDURALIFE-powered CRT-Ds.

2.2 Overview of Company's description of ongoing studies

The Company identifies two ongoing studies of ENDURALIFE-powered CRT-D devices.

The Company reports that it is conducting a prospective, non-comparative single arm observational cohort study (n = 1600) to assess the rate and cause of device replacements for Boston Scientific ICDs and CRT-Ds at 5 years post-implantation (anticipated publication May 2021). Although relevant to the scope, this study will not be ready for publication within the guidance development timeframe.

The company also makes reference to the UK British Heart Rhythm Society/NICOR Cardiac Rhythm Management National Clinical Audit registry focusing on device longevity.

In addition the EAC identified three additional ongoing studies, none of which are directly relevant to the decision problem. These are shown for reference in Appendix 1 and do not otherwise contribute to this report.

2.3 Critique of Company's definition of the decision problem

Population

With regard to population, the clinical evidence submitted by the Company has a high degree of applicability to the Scope. All cited studies are of people with heart failure and the included longevity studies present the cardiac morbidity of the study participants, indicating that they represent the population specified in the scope.

Intervention

The intervention studied in the clinical evidence submitted by the Company fits the scope. Although some longevity studies study ICDs as a wider group of devices, rather than only CRT-Ds, they present adequate data on the CRT-D subgroup to enable comparisons of CRT-D devices across manufacturers.

EAC Description of a CRT-D device

A CRT-D device is an implantable medical device used to increase cardiac output in selected patients with heart failure, and also to correct occasional, life threatening arrhythmias.

Implantation of a CRT-D device is usually done in a cardiac catheterisation lab under local anaesthetic. The heart is visualised using fluoroscopy to provide a continuous image on a screen. A catheter is introduced to a vein beneath the collar bone then the leads are introduced through the catheter until the lead tips are correctly placed in the right atrium, right ventricle and external to the left ventricle via the coronary sinus vein (see technical assessment). An incision is made in the skin beneath the collar bone to create a pocket underneath the subcutaneous fat. The generator is connected to the leads and is placed in the pocket before the incision is closed.

Once functioning, the CRT-D device continuously monitors the electrical activity of the heart and in response provides cardiac resynchronisation therapy, meaning that it provides electrical pulses to ensure that the two ventricles contract together in a coordinated fashion. This places a frequent, but relatively small demand for power on the battery. When the device detects

a dangerous arrhythmia (ventricular tachycardia or ventricular fibrillation) the CRT-D delivers a cardioversion 'shock' to the heart to restore normal sinus rhythm. This occurs less frequently in most patients but places a large demand for battery power. In addition shocks may be distressing for patients, so careful counselling is provided when CRT-D is considered as a therapy for heart failure.

ENDURALIFE-powered CRT-D devices

The company's submission states that the following Boston Scientific CRT-D devices are powered by the ENDURALIFE battery technology:

COGNIS™ CRT-D Family

ENERGEN™ CRT-D Family

PUNCTUA™ and PUNCTUA™ NE CRT-D Family

INCEPTA™ CRT-D Family

AUTOGEN™ CRT-D Family

INOGEN™ CRT-D Family

DYNAGEN™ CRT-D Family

ORIGEN™ CRT-D Family

Regulatory approval

All of the above devices may be marketed in the European Union. For CE marking purposes the COGNIS device has Design-Examination Certificate no. CE531475 for conformity with EC Council Directive 90/385/EEC Annex 2 Section 4. For the INCEPTA, ENERGEN, PUNCTUA NE and PUNCTUA CRT-Ds the Design-Examination Certificate no. is CE566332 and for the AUTOGEN, DYNAGEN, ORIGEN and INOGEN CRT-Ds the Design-Examination Certificate no. is CE602838.

These CRT-D devices are often referred to as 'the generator', and the generator is implanted with three leads which conduct electrical energy from the generator to the heart muscle. The leads are separate medical devices requiring their own regulatory approval.

Comparator(s)

The comparators are CRT-D devices that are not powered by the ENDURALIFE battery technology. In terms of evidence, this is represented

broadly by head-to-head comparisons of CRT-Ds from different manufacturers, of which, based on marketing information and published studies there are four:

- St Jude Medical
- Medtronic
- Biotronik
- Sorin (now Liva Nova)

All of the studies provide as comparator, CRT-Ds from the above companies. Some studies include other types of cardiac implantable electrical devices (CIEDs) in addition to CRT-Ds.

Outcomes

The six submitted studies of longevity report the following outcome measures:

- Rate of replacement due to battery depletion (device reaching ERI)
- Time to battery depletion (ERI)
- % battery survival at successive years' follow-up
- Reasons for devices being out of service (mortality, heart transplantation, device revision/replacement (including due to infection), device or lead failure)
- Factors associated with device longevity

In addition the studies report CRT-D operating parameters which are either a 'fixed quantity' for that device, or that are a result of interaction between the device, the leads and the patient. These are reported because they may influence the rate of battery discharge and hence battery life and hence device longevity. These factors are addressed in the EAC's Technical Assessment.

PPR data suggest that the biggest driver of device longevity is normal battery depletion, rather than device malfunction.

Cost analysis

The cost analysis in the Company's submission matches the cost analysis specified in the final scope.

Subgroups

No subgroups are specified in the Scope or reported in the Company's submission. Some studies present data on a subgroup CRT-Ds considered to be newer generation devices at the time of publication: this reflects the timing of the study recruitment periods and it is generally the case that the 'newer generation' subgroup broadly contains the ENDURALIFE-powered CRT-Ds.

Special considerations, including issues related to equality

The published studies suggest that people who undergo implantation with CRT-D devices are, on average, elderly and predominantly male. The EAC does not anticipate that this is indicative of inequity of access to treatment, but expects that the study samples reflect the epidemiology of heart failure.

3 Clinical evidence

3.1 Critique of the Company's search strategy

The Company conducted two searches for published literature on:

- studies of device longevity
- the incidence of complications associated with device replacement and outcomes relating to patient quality of life or satisfaction associated with device replacement.

For the search of studies of device longevity the Company did not search all the databases that are recommended in the Company template, no explanation was provided. The Company searched the following databases and sources: PubMed; Cochrane; ClinicalTrial.gov and libraries held by the Company.

The strategies used for the searches of PubMed and Cochrane were assessed in accordance with the PRESS checklist (Peer Review of Electronic Search Strategies). The strategies used were simplistic, did not incorporate subject headings and did not contain a broad selection of terms or reflect the intervention described in the PICO. The Company limited the search to studies published from 2008 which is in keeping with the first commercial launch of the technology.

The search of ClinicalTrial.gov is appropriate to identify 'Ongoing and Completed' trials but would only identify studies that are registered as a clinical trial. From searches conducted by the EAC we believe that the only relevant ongoing trial has been identified.

The Company's library is likely to be a good repository of studies for this technology and probably contains all the relevant studies. The Company also collected abstracts, congress publications and other external communications but no details were provided as to how this was done.

For the clinical evidence there were a limited number of records identified which reflects the simplicity of the search. The Company conducted a separate search for outcomes related to device replacement which retrieved significantly more records. This search was simplistic and likely to overlap with the search for clinical evidence. The two searches could have been incorporated into one search.

A further search method that the Company could have conducted to ensure that all relevant studies had been identified would have been to citation track the selected included publications.

The Company included adverse events that were reported in the MAUDE database but no details were provided on the search. It should be noted that Medical Device Reports (MDRs) within the MAUDE database are collated as

a result of a passive surveillance system that has limitations such as the potential submission of incomplete, inaccurate, untimely, unverified or biased data.

However despite some inadequacies of the search methods we believe that the Company has identified all the relevant literature for this technology at the time of writing their report.

3.2 Critique of the Company's study selection

The Company presents a flow diagram of study selection (as per PRISMA statement) and has selected appropriate studies reporting longevity of ENDURALIFE-powered CRT-D devices compared to comparator devices implanted in a contemporary period.

Study selection criteria were consistent with the Scope, for example the Company took the reasonable step of excluding studies where ENDURALIFE-powered CRT-Ds comprised less than 50% of devices studied. Inclusion of the von Gunten study is an exception, since in this study only 39% of Boston Scientific CRT-Ds are powered by the ENDURALIFE battery technology. However a supplement to this paper reports longevity for 76 ENDURALIFE-powered COGNIS CRT-Ds. The remainder of the studies of CRT-D longevity include participants who underwent implantation from 2008 onwards i.e. the point from which ENDURALIFE battery technology became available, whereas the von Gunten study [6], included people implanted between 1994 and 2014.

3.3 Included and excluded studies

The Company's submission of clinical evidence comprises three main categories of clinical evidence: published studies reporting longevity, Product Performance Reviews (PPRs) produced by manufacturers and studies reporting complication rates following replacement of CIEDs.

Published studies comparing CRT-D longevity across manufacturers

The company includes six case series studies of CRT-D device longevity reported in seven sources [1-7]: four studies are published in full as journal articles [1-4;6]. Of these, one study is reported in two papers at different follow-up points [1;2] Two studies are reported only as conference abstracts [5;7]. All analyses are retrospective. For ease of reference we will refer to these studies by their first author's names as follows:

- Alam [1;2]
- Ellis [3]

- Landolina [4]
- Lau [5]
- von Gunten [6]
- Williams [7]

Table 1 presents an overview of the key features of these studies.

Product Performance Reviews

The five PPRs were produced by the five 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. PPRs aim to report device malfunctions in a standard format and are based only on data derived from explanted devices returned to the manufacturer. Return rates are acknowledged to be less than 100%.

Published studies reporting complications due to replacement procedures

The manufacturer's submission contained 19 studies that highlight the complications associated with ICD and CRT-D replacement; these were not device or manufacturer specific. These are references 29-47 in the Company's submission of evidence. Only one of these studies was used by the company to provide inputs to the economic model [8].

The EAC sought advice from clinical experts which identified a Danish Cohort study [9] as the best source of evidence on complications following de novo and replacement implant procedures.

Patient preference

One additional submitted study investigated the patient's perspective on device size compared to device longevity [10].

Table 1. Characteristics of 7 published observational studies reporting battery survival

Study & country	Patient population	CRT-D devices studied	Study design	Sample size	EAC comments
Alam 2016 USA Full journal article	Patients implanted with CRT-D between 1 Jan 2008 and 31 Dec 2010: (last access to patient record 20 Dec 2015): Boston Scientific: 173 Medtronic: 391 St Jude Medical: 57 **Gender** Male: 484/652 = 74% Female: 168/652 = 26% **Age** Mean 69 (SD 3) years **Cardiac morbidity** CHD 64% LVEV 29 (SD 12) %	As per Alam 2014 below, but subject to additional loss to follow-up.	Retrospective cohort, single centre (University of Pittsburgh Medical Center) reported as full journal article. This is an update of the same cohort reported by Alam et al. 2014 cited below.	**Included** Total n = 621 Boston Scientific: 173 (28%) Medtronic: 391 (63%) St Jude Medical: 57 (9%) **Excluded** Boston Scientific: 31 Medtronic: 55 St Jude Medical: 8 Biotronik 6 Exclusions were due to follow-up loss, change of follow-up provider or due to small numbers of	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) must 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.

Study & country	Patient population	CRT-D devices studied	Study design	Sample size	EAC comments
	Paced QRS width mean 155 (SD 29) ms			implants (Biotronik).	
Alam 2014 USA Full journal article (earlier report of same study as Alam 2016, above)	Patients implanted with CRT-D between 1 Jan 2008 and 31 Dec 2010 (last access to patient record 15 Apr 2013): Boston Scientific: 173 Medtronic: 416 St Jude Medical: 57 **Gender** Male: 484/652 = 74% Female: 168/652 = 26% **Age** Mean 69 (SD ±13) years **Cardiac morbidity** CHD 64%	**Boston Scientific:** ENDURALIFE-powered CRT-Ds: N118 COGNIS 100-D (22) N119 COGNIS 100-D (100) Other: 51 **Medtronic:** 8042 InSync III: (6) C154DWK Concerto: (178) C154VWC Concerto (1) D224TRK Consulta (227) D274TRK Concerto II (1) D284TRK Maximo II (3) **St Jude Medical:** 3207-30 (3) 3207-36 (37) CD3211-36 (14) CD3215-36Q (1) 3211-36 (1) 3211-36Q (1)	Retrospective cohort, single centre (University of Pittsburgh Medical Center) reported as full journal article.	**Included** Total n = 646 Boston Scientific: 173 (27%) Medtronic: 416 (63%) St Jude Medical: 57 (9%) **Excluded n = 100:** Boston Scientific: 32 Medtronic: 55 St Jude Medical: 7 Biotronik 6 Exclusions were due to follow-up loss, change of follow-up provider or due to small	Full journal article. 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.

Study & country	Patient population	CRT-D devices studied	Study design	Sample size	EAC comments
	LVEV 29 (SD ±12) % Paced QRS width mean 155 (SD ±29) ms			numbers of implants (Biotronik).	
Ellis 2016 USA	1302 Patients (NYHA Class II-IV) implanted with CRT-D between 1 Aug 2008 and 31 Dec 2010 (last data entry 31 Dec 2014): **Gender** Male: 73% (n=950/1302) Female: 27% (n=352/1302) **Age** Mean 68.1 (SD ±11.8) years **Cardiac morbidity** Mean LVEF 25.1% (SD ±10.1%) Mean QRS duration 152.0 (SD	Device names not reported.	Retrospective multicentre study (Vanderbilt Heart and Vascular Institute) reported as full journal article.	Total n = 1302 BSC: n = 322 (24.7%) MDT: n = 794 (60.9%) SJM: n = 186 (14.2%)	Full journal article. Authors report that the proportion of devices by manufacturer represents the market share distribution. No exclusions are reported.

<table>
<tr><th>Study & country</th><th>Patient population</th><th>CRT-D devices studied</th><th>Study design</th><th>Sample size</th><th>EAC comments</th></tr>
<tr><td></td><td>±25.6) ms
Reason for implantation:
Ischaemic cardiomyopathy 56.3% (n=731/1299))
Nonischaemic cardiomyopathy 41.9% (n=544/1299)
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%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Landolina 2015

Italy</td><td>1726 patients with heart failure implanted with CRT-D devices between Jan 2008 and Mar 2010 (data accessed March 2014).</td><td>
<table>
<tr><th>Manufacturer</th><th>Device</th><th>Release</th><th>Battery chemistry</th><th>Capacity</th><th>n</th></tr>
<tr><td rowspan="8">Biotronik</td><td>Lumax 300</td><td>2006</td><td>Li/MnO2</td><td>1.28Ah</td><td>3</td></tr>
<tr><td></td><td></td><td>Li/CFx-SVO</td><td>1.72Ah</td><td></td></tr>
<tr><td>Lumax 340</td><td>2006</td><td>Li/MnO2</td><td>1.28Ah</td><td>26</td></tr>
<tr><td></td><td></td><td>Li/CFx-SVO</td><td>1.72Ah</td><td></td></tr>
<tr><td>Lumax 540*</td><td>2008</td><td>Li/MnO2</td><td>1.72Ah</td><td>20</td></tr>
<tr><td></td><td></td><td>Li/CFx-SVO</td><td>1.72Ah</td><td></td></tr>
</table>
</td><td>Retrospective cohort study of nine centres reported as full journal article.</td><td>n = 1726

CRT-D devices:
Biotronic n = 49 (3%)
Boston Scientific n =</td><td>Full journal article. 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</td></tr>
</table>

<table>
<tr><th>Study & country</th><th>Patient population</th><th>CRT-D devices studied</th><th>Study design</th><th>Sample size</th><th>EAC comments</th></tr>
<tr>
<td></td>
<td>Gender/age not reported.

Implantation type:
De novo: n = 1071 (62%)
Replacement: n = 472 (27%)
Upgrade: n = 183 (11%)</td>
<td>
<table>
<tr><td>Boston Scientific</td><td>Renewal</td><td>2004</td><td>Li/SVO</td><td>2.00Ah</td><td>288</td></tr>
<tr><td></td><td>Livian</td><td>2007</td><td>Li/CFx-SVO</td><td>1.86Ah</td><td>29</td></tr>
<tr><td></td><td>Cognis*</td><td>2008</td><td>Li/MnO2</td><td>1.84Ah</td><td>291</td></tr>
<tr><td>Medtronic</td><td>InSync III Marquis</td><td>2003</td><td>Li/SVO</td><td>0.90Ah</td><td>67</td></tr>
<tr><td></td><td>InSync Sentry</td><td>2004</td><td>Li/SVO</td><td>0.89Ah</td><td>7</td></tr>
<tr><td></td><td>InSync Maximo</td><td>2005</td><td>Li/SVO</td><td>0.89Ah</td><td>21</td></tr>
<tr><td></td><td>Concerto</td><td>2006</td><td>Li/SVO</td><td>1.00Ah</td><td>171</td></tr>
<tr><td></td><td>Consulta*</td><td>2008</td><td>Li/SVO</td><td>1.00Ah</td><td>447</td></tr>
<tr><td></td><td>Maximo II*</td><td>2008</td><td>Li/SVO</td><td>1.00Ah</td><td>69</td></tr>
<tr><td></td><td>Protecta*</td><td>2010</td><td>Li/SVO</td><td>1.00Ah</td><td>16</td></tr>
<tr><td>Sorin</td><td>Ovatio</td><td>2005</td><td>Li/SVO</td><td>0.87Ah</td><td>30</td></tr>
<tr><td></td><td>Paradym*</td><td>2008</td><td>Li/CFx-SVO</td><td>1.96Ah</td><td>69</td></tr>
<tr><td>St Jude Medical,</td><td>Atlas</td><td>2003</td><td>Li/SVO</td><td>b</td><td>40</td></tr>
<tr><td></td><td></td><td></td><td>Li/SVO</td><td>b</td><td></td></tr>
<tr><td></td><td>Epic</td><td>2006</td><td>Li/SVO</td><td>b</td><td>26</td></tr>
<tr><td></td><td>Promote*</td><td>2007</td><td>Li/SVO</td><td>b</td><td>106</td></tr>
<tr><td></td><td></td><td></td><td>Li/SVO</td><td>b</td><td></td></tr>
</table>
* considered to be ‘new generation’

All devices were programmed to deliver true biventricular pacing.
</td>
<td></td>
<td>608 (35%)
Medtronic n = 798 (46%)
Sorin n = 99 (6%)
St Jude Medical n = 172 (10%)

146 (8%) patients were censored since they chose to receive follow-up at non-study centres.</td>
<td>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 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</td>
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<table>
<tr><th>Study & country</th><th>Patient population</th><th>CRT-D devices studied</th><th>Study design</th><th>Sample size</th><th>EAC comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>include COGNIS devices i.e., 100% ENDURALIFE-powered CRT-Ds.</td></tr>
<tr><td>Lau 2015

UK</td><td>Patients with CRT-Ds implanted in 2008-9.</td><td>
<table>
<tr><th>Manufacturer</th><th>Device</th><th>Battery chemistry</th><th>Total capacity (Ah)</th><th>Usable capacity (Ah)</th><th>Ratio</th></tr>
<tr><td>Boston Scientific</td><td>Cognis n=27</td><td>LiMnO2</td><td>2</td><td>1.8</td><td>0.9</td></tr>
<tr><td>St Jude Medical</td><td>Promote/Atlas HF n=66</td><td>LiSVO</td><td>1.87</td><td>1.31</td><td>0.7</td></tr>
<tr><td>Medtronic</td><td>Consulta/Concerto Maximo n=62</td><td>LiSVO</td><td>1.4</td><td>1</td><td>0.7</td></tr>
</table>
</td><td>Single centre case series reported as a conference abstract.</td><td>n = 321</td><td>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.</td></tr>
<tr><td>von Gunten 2015

The Netherlands / Switzerland</td><td>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.</td><td>Boston Scientific CRT-D devices studied (n = 259):
<table>
<tr><td>Device</td><td></td><td></td></tr>
<tr><td>Cognis CRT</td><td>76</td><td>1</td></tr>
<tr><td>Contak CD 1823</td><td>11</td><td>4</td></tr>
<tr><td>Contak Renewal 2 H155</td><td>30</td><td>16</td></tr>
<tr><td>Contak Renewal 4 190</td><td>1</td><td>1</td></tr>
<tr><td>Contak Renewal 4 AVT M177 HE</td><td>23</td><td>13</td></tr>
<tr><td>Contak Renewal 4 H195</td><td>15</td><td>8</td></tr>
<tr><td>Contak Renewal 4 HE H199</td><td>14</td><td>10</td></tr>
<tr><td>Contak Renewal 4 RF H230</td><td>31</td><td>10</td></tr>
<tr><td>Contak Renewal 4 RF H235</td><td>9</td><td>2</td></tr>
<tr><td>Contak Renewal H135</td><td>21</td><td>15</td></tr>
<tr><td>Energen CRT</td><td>24</td><td>0</td></tr>
<tr><td>Energen DR</td><td>9</td><td>0</td></tr>
</table>
</td><td>Retrospective cohort study (2 centres: Erasmus, Netherlands, Basel, Switzerland).</td><td>3436 patients in total, of which:
2154 were alive in the study as of 5 June 2014
822 died
85 underwent transplant</td><td>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 morbidity, NYHA class, medical therapies) for</td></tr>
</table>

Study & country	Patient population	CRT-D devices studied	Study design	Sample size	EAC comments
	Data last accessed: 31 May 2014 (Erasmus), 30 June 2014 (Basel). N (CRT-D devices) = 1284/ = 26% N (BSC CRT-D devices) = 102/259 = 39%" **Gender** Male: 2721/3436 = 79% **Age** Mean 59 (SD±14) years **Cardiac morbidity** Mean LVEF 32 % (SD±13%) Mean QRS duration 127 (SD ±35) ms Ischaemic cardiomyopathy 74%	**Energen VR** **28** **0** **Incepta F 162** **2** **0** **Incepta P 163** **1** **0** **Incepta P 165** **1** **0** Teligen CRT 2 0 Teligen DR 28 0 Teligen VR 82 0 Ventak Mini 4 1793 34 22 Ventak Prizm 1850 4 4 Ventak Prizm 2 1851 9 7 Ventak Prizm 2 1860 35 26 Ventak Prizm 2 1861 46 29 Ventak Prizm AVT 1900 5 3 Ventak Prizm HE 1852 28 23 Ventak Prizm HE 1853 22 15 Vitality 1871 65 38 Vitality 2 EL 9 0 Vitality 2 EL T177 48 10 Vitality 2 T165 77 20 Vitality 2 T175 142 21 Vitality A 155 3 1 Vitality VR 1870 12 12 Of the above 141 shown in **bold** 102 are ENDURALIFE-powered CRT-D devices.		154 were lost to follow-up 32 were downgraded or not replaced.	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.

Study & country	Patient population	CRT-D devices studied	Study design	Sample size	EAC comments
Williams 2014 USA	90 patients with CRT-Ds implanted between 1 July 2008 and 31 July 2010. **Gender:** not reported **Age:** mean 72 (SD ±9) years **Cardiac morbidity:** Mean creatinine,1.3 (SD ±0.5) mg/dl Mean ejection fraction 0.25 (SD ±0.08) %	Device names not reported.	Retrospective cohort at a single nonacademic community hospital reported as a conference abstract.	Total (n = 90) Boston Scientific (n = 53) Medtronic (n = 28) St Jude Medical (n = 10).	Study available in abstract only: full details not reported, including values for some outcome data.

3.4 Overview of methodologies of all included studies

Published studies comparing CRT-D longevity across manufacturers

The EAC has critiqued the six studies of CRT-D longevity, considering these key evidence against which the company's claimed benefits may be judged. For the studies published as full journal articles, critical appraisal checklists are included in Appendix 3. An overview of study characteristics is provided here and Table 3 shows the key features of each individual study of CRT-D longevity.

Population

The studies of longevity are retrospective analyses of case series originating from the USA, Europe and the UK. The patient samples studied have a majority of male participants (73-79% where reported) and average age at implantation, where reported, has range 59-72 years. Sample demographic details appear to be consistent across the studies and most likely reflect the epidemiology of heart failure. Most of the studies provide details of cardiac morbidity at entry to the study (Table 1).

Study size

The three largest studies [3;4;6] report on over 1000 CRT-D s, the largest being the Landolina study (n = 1726) [4]. The three smaller studies have CRT-D sample sizes ranging from 90 to 621 participants [1;2;5;7].

Intervention

All of the six longevity studies [1-7] evaluate CRT-D devices (Table 2). In the von Gunten study [6], only 26.3% of devices studies are CRT-Ds, however the results are presented distinctly for this subgroup (n = 1284 devices) so the data are useable. The remainder of devices in this study are other CIEDs: VVI-ICDs (44.2%), DDD-ICDs (27.4%) and subcutaneous ICDs (2%), which are not part of the decision problem. However a supplement to this paper reports longevity for 76 ENDURALIFE-powered COGNIS CRT-Ds.

All of the studies recruited participants undergoing de novo CRT-D implantation and in addition, the Ellis study includes a proportion of patients undergoing device replacement / revision procedures (44%) as did the Landolina study (38%).

The vast majority of CRT-Ds studied are provided by five manufacturers. Of these three (Boston Scientific, Medtronic, St Jude Medical) are better represented in the studies, and two (Sorin (non Liva Nova) and Biotronik) have fewer CRT-D cases included in the studies. There is therefore much less

published, empirical data on the longevity of Sorin/Liva Nova and Biotronik CRT-Ds, however PPR data exist for all devices (see Sections 3.3. and 3.6).

Authors of longevity studies do not report reasons why a particular manufacturer's CRT-D device was implanted according to patient factors. However the Ellis study notes a trend by which patients undergoing de novo implantation were more likely to receive Boston Scientific (2.0 Ah battery capacity) CRT-Ds whereas patients undergoing replacement procedures were more likely to receive Medtronic (1.0 Ah battery capacity) CRT-Ds, (p = 0.053).

A limitation of some of the studies is that not all Boston Scientific CRT-Ds are powered by the ENDURALIFE battery technology, thus limiting applicability to the decision problem. The proportion of Boston Scientific CRT-Ds is shown below: this limitation is compounded by the fact that it is the studies published in full that have this limitation to a greater degree: in von Gunten only 39% of Boston Scientific CRT-Ds are ENDURALIFE-powered CRT-Ds. However a supplement to this paper reports longevity for 76 ENDURALIFE-powered COGNIS CRT-Ds.

In some instances the company has requested and received personal communication from authors to ascertain the proportion of Boston Scientific devices that were powered by ENDURALIFE battery technology. For example this was not reported in the Ellis study, whereas the company submission reports that 97% of Boston Scientific CRT-Ds were ENDURALIFE-powered CRT-Ds.

Table 2: proportion of devices in longevity studies that are CRT-Ds

Study	**% CRT-D (entire study cohort)**	**% of Boston Scientific CRT-Ds studied that are ENDURALIFE-powered CRT-Ds**	**Is longevity reported for the CRT-D subgroup?**
Alam [1;2]	100%	122/173 = 70.5% (as reported in the paper) 122/188 = 64.9% (as advised by the company)	N/A
Ellis [3]	100%	Not reported in study, though implant period is coterminous	N/A

		with the period since market launch of ENDURALIFE battery technology. The Company's submission states that 312/322 = 97% of BSC devices were ENDURALIFE-powered CRT-Ds.	
Landolina [4]	100%	291/608 = 47.9% (paper also reports on a subgroup of modern generation devices including the ENDURALIFE-powered CRT-Ds (n = 291)	N/A
Lau [5]	100%	100%	N/A
von Gunten [6]	1284/4881 = 26.3%	102/259 = 39.4% Reports separately for 76 ENDURALIFE-powered COGNIS CRT-Ds.	Yes
Williams [7]	100%	Not reported. Company's submission states 51/53 = 96.2%	N/A

The Company uses, in the economic model, the Landolina data for the latest generation of CRT-Ds in the study period (Landolina 2016, unpublished). These are the subgroup of ENDURALIFE-powered COGNIS CRT-Ds (note: both Landolina papers are derived from the same series of patients. It is unclear why in the first paper [4] there are 291 COGNIS devices and in the second paper (Landolina 2016, unpublished) there are 376 COGNIS devices). The EAC accepts that the Landolina data represent ENDURALIFE-powered CRT-Ds.

Follow-up

Average follow up in the six longevity studies ranges from 3.4-4.4 years. The latest point of follow-up for reporting of CRT-D longevity is at 6 years in the Lau study, available as an abstract only [5].

Analysis method

The longevity studies use actuarial methods to analyse cumulative survival probability e.g. Kaplan-Meier, with statistical significance assessed with the log-rank test. The analysis typically censors patients for competing events, including death, device replacement for infection or generator/lead malfunction and heart transplantation (Alam 2014). Covariates that can affect time to battery depletion are typically analysed using a Cox proportional hazards model. (Alam 2014).

In contrast to PPRs (see below) the device survival longevity studies consider any type of battery depletion, regardless of whether it is normal or premature.

Outcomes

The studies report battery depletion (ERI) without reference to whether this is classified as premature, versus normal battery depletion (the definition applies only to PPRs and is discussed in Section 3.4). In practical terms this is not a limitation; the PPRs demonstrate that malfunctions, including premature battery depletion, are rare events.

Methodology: published studies reporting complications due to replacement procedures

Of the 19 studies included in the Company's submission, three [8;11;12] are systematic reviews which include data from the majority of the same body of primary studies. To avoid presenting the same data twice, The EAC selected the three systematic reviews plus two primary studies [13;14] not included in the systematic reviews, for consideration as evidence on complications.

One of these primary studies [14] is an analysis of health care claims data from the Truven Health analytics MarketScan Commercial Research Database in the US, based on 45,252 patients who underwent CIED replacement.

The second primary study [13] utilised patients enrolled on the ALTITUDE project, an initiative to prospectively analyse data obtained from implanted Boston Scientific ICD and CRT devices, including 7458 cases ICD generator replacement.

The Danish cohort study identified by clinical experts [9] is a large, retrospective analysis of a cohort of 5918 patients who underwent a CIED procedure in 14 centres in Denmark between May 2010-April 2011. Because a clinical expert plus the EAC consider this to be a robust source of data on

complications associated with CRT-D replacement, the EAC undertook data extraction (Tables 11-13) and critical appraisal (Appendix 4).

The EAC considers applicability to CRT-D replacement procedures is limited only to a small extent by the inclusion of data for replacement of ICDs because in either case the procedure is essentially the same.

Table 3: Study characteristics of Danish retrospective cohort study [9]

Study & country	Patient population	CRT-D devices studied	Study design	Sample size	EAC comments
Kirkfeldt 2014 Denmark	5918 patients who underwent a CIED procedure between May 2010-April 2011 **Gender** Male: 3707/5918 = 63% Female: 2211/5918 = 37% **Age** Median 74 (IQR 65-83) years **CIED type** Single-chamber PM: 1160/5918 (20%) Dual-chamber PM: 3029/5918 (51%) CRT-P: 209/5918 (4%) Single-chamber ICD: 684/5918 (12%) Dual-chamber ICD: 391/5918 (7%) CRT-D: 445/5918 (8%) **Procedure type** New implant: 4355/5918 (74%) Generator replacement: 1136/5918 (19%) System upgrade or lead revision: 427/5918 (7%)	Device names not reported	Retrospective cohort, multi-centre (14 centres in Denmark.	**Included** Total n = 5918 **Excluded** Patients with epicardial systems (n=24).	Full journal article. No exclusion criteria were listed and the only inclusion criterion was patients who underwent a CIED procedure. Complications were presented for device type but were not manufacturer specific.

Methodology: Product Performance Reviews

The US Heart Rhythm Society Task Force recommended production of PPRs for all market-approved implantable cardiac pulse generators or leads. PPR production has been taken up by all manufacturers of CRT-D devices. The international standard ISO 5841-2:2014 (E) specifies the required content of PPRs. The EAC accessed the relevant British standard: BS ISO 5841-2:2014 in order to understand the process behind PPR production. Annex A of this standard defines the statistical method for device survival analysis.

Production of PPRs 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. Annex A of BS ISO 5841-2:2014 defines the following categories that apply to a CRT-D device following implantation:

- Category A: Device that is in service. No complication recorded or malfunction confirmed by returns analysis.
- Category B: Device removed from service for reasons not related to the functioning of the device. No complication recorded or malfunction confirmed by returns analysis.
- Category C1: Devices with a malfunction confirmed by returned product analysis or leads with a reported complication.
- Category C2: Pulse generator battery depleted. No malfunction confirmed by returns analysis.
- Category D: Patient has died. However, the death, as far as can be verified, is unrelated to the functioning of the device. No complication recorded or malfunction confirmed by returns analysis.
- Category L: Device is lost to follow-up. No complication recorded or malfunction confirmed by returns analysis.

Based on knowledge of the status of CRT-D devices observed during follow-up and at device return, actuarial statistical methods are used to derive a cumulative survival probability. Thus comparison of PPRs across manufacturers may permit comparisons of CRT-D longevities.

PPRs report survival probability in two ways; both are based on real, observed data. Firstly survival probability can include survival free from both malfunction and normal battery depletion. Secondly survival probability is also

reported as survival free of malfunction alone leading to explantation i.e. 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 market. It is important to note that this occurs under specific, controlled conditions which may not necessarily occur in clinical use. The specific controlled conditions also differ by manufacturer.

'Normal battery depletion' is defined in BS ISO 584-2:2014 as follows: "(a)....implant time that meets or exceeds the nominal (50 percentile) predicted longevity at default (labelled) settings, or (b) a device is returned and the device has reached its elective replacement indicator(s) with implant time exceeding 75% of the expected longevity using the longevity calculation tool available at time of product introduction, calculated using the device's actual use conditions and settings.

Note that failure of a CRT-D due to early battery depletion, i.e. not meeting the criteria for normal battery depletion above, is always considered a malfunction.

The EAC discussed with the company the methods used in the production of PPRs and acknowledges that PPRs have limitations in enabling direct comparisons between companies as follows:

- Boston Scientific PPRs are based on implants within the US due to a higher level of reporting within the US than internationally. Malfunctions of devices from other countries are recorded, but they are not used in the survival calculations in PPRs. However the Company considers the US data to be generally representative for worldwide performance of Boston Scientific CRT-Ds.

- 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, between 58% and 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 Category A, above, instead of Category L (lost to follow-up). This would overestimate CRT-D longevity. Neither the company nor the EAC is aware of any data on how well the different manufacturers correctly classify CRT-Ds that are either still in service or lost to follow-up.

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

3.5 Overview and critique of the Company's critical appraisal

The company has completed critical appraisal checklists for the included studies. These confirm that the studies are acceptable evidence, though they do not bring out the key features of the evidence, which is discussed elsewhere in the company's submission and in this report.

3.6 Results

Published studies comparing CRT-D longevity across manufacturers

All of the published retrospective studies of CRT-D longevity in the Company's submission, presenting head-to-head comparisons of CRT-D devices from different manufacturers, provide evidence that the ENDURALIFE-powered CRT-D devices have better longevity than comparator CRT-D devices. The six studies of CRT-D longevity [1-7] have an average (mean or median) follow-up of between 3.0 years [3] and 6 years [5]. Four of the studies are published as full journal articles [1-4;6], with an average (mean or median) follow-up period of between 3.0 years [3] and 4.4 years [6].

The Landolina study [4] and the von Gunten study present results for the sub group of CRT-Ds considered as 'recent generation' (defined as market release date 2007 onwards in the Landolina study and as implant date from 2006 onwards in the von Gunten study). These analyses demonstrate that CRT-D longevity improved over time, however the recent generation CRT-Ds studied, implanted between 2008-2010 (Landolina) and 2006-2014 (von Gunten) may have been superceded by devices marketed today.

Alam [1;2]

In the most recent publication from the study by Alam et al. with a mean follow-up of 3.4 years, rates of CRT-D replacement due to battery depletion

were Boston Scientific: 16%, St Jude Medical: 53%, Medtronic: 51%; p<0.001. The hazard ratios for battery depletion (adjusted for unbalanced electrical pacing parameters) were as follows: Boston Scientific:Medtronic 0.11 (95% CI 0.07,0.16) p < 0.001, Boston Scientific:St Jude Medical 0.25 (95% CI 0.13, 0.47) p < 0.001. Among patients with six years follow-up rates of battery survival were BCS: 77%, St Jude Medical: 44%, Medtronic: 10%.

Ellis [3]

In the study by Ellis et al. at a mean follow-up of 3.0 (SD 1.3) years, rates of CRT-D devices reaching ERI were as follows: Boston Scientific: 0.30%, St Jude Medical: 3.8%, Medtronic: 13.5%. Mortality rates in each manufacturer group were: Boston Scientific: 28.0%, St Jude Medical: 16.7%, 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 [4]

The study by Landolina et al. had a median follow-up of 3.6 (IQR 1.5, 4.4) years. Rates of battery depletion were as follows: Boston Scientific: 18%, St Jude Medical: 20%, Medtronic: 29%, Biotronik: 20%, Sorin: 20%. Rates of CRT-D device replacement (any cause) were as follows: Boston Scientific: 22%, St Jude Medical: 24%, Medtronic: 34%, Biotronik: 20%, Sorin: 22%. Mortality rates were as follows: Boston Scientific: 18%, St Jude Medical: 16%, Medtronic: 14%, Biotronik: 12%, Sorin: 14%. Among CRT-D devices classified as recent generation (for the most part released to market after 2007) and excluding Biotronic CRT-Ds and Sorin CRT-Ds due to there being fewer than 100 implants: the rates of devices still in service at five years were as follows: Boston Scientific: 88%, St Jude Medical: 75%, Medtronic: 52%; p<0.01. In multivariate analysis, factors associated with CRT-D replacement due to battery depletion were: manufacturer: HR Boston Scientific:Medtronic 0.64, 95% CI 0.47,0.89, p = 0.008; recent generation device: HR recent:older 0.57, 95% CI 0.45, 0.72, p = 0.001; Battery chemistry: HR Li/MnO_2:Li/SVO 0.37, 95% CI 0.22,0.64 p = 0.001; HR Li/CFx-SVO:Li/SVO 0.28, 95%CI 0.16, 0.50, p = 0.001; High left ventricle lead output (pulse amplitude > 2.5V, duration > 0.5 ms) HR high:low 1.96, 95% CI 1.57,2.46, p = 0.001; unipolar left ventricle lead: HR unipolar:non-unipolar 1.58, 95% CI 1.25, 2.01, p = 0.001.

von Gunten [6]

The study by von Gunten et al. had a median follow up of 4.4 (IQR 2,7.3) years. Rates of CRT-D replacement were Boston Scientific: 30.9%, St Jude Medical: 22.1%, Medtronic: 36.3%, Biotronik: 10.1%, Sorin: 0%, (a total of 4

Sorin CRT-Ds were studied). In devices implanted from the year 2006 onwards, five year longevity rates were as follows: Boston Scientific: 97.6%, St Jude Medical: 45.3%, Medtronic: 74.1%, Biotronik: 76.2%. Also in devices implanted from the year 2006 onwards, six year longevity rates were as follows: Boston Scientific: 97.6, St Jude Medical: 26.5, Medtronic: 46.3, Biotronik: 44.9. The rate of five year overall survival in patients with CRT-Ds (all manufacturers) was 72.8%. The rate of five year longevity of CRT-Ds implanted from 2006 onwards (all manufacturers) was 66.3%. In the sub group of 76 ENDURALIFE-powered COGNIS CRT-Ds there was 1 replacement representing 97.5% longevity at 4 years following implantation.

Lau [5]

This study is available as an abstract. At six years follow up Boston Scientific CRT-D devices had 100% survival. St Jude Medical CRT-Ds began to reach ERI after 2.8 years and Medtronic CRT-Ds after 2.5 years.

Williams [7]

This study is available as an abstract. At four years follow up the rates of CRT-D devices reaching ERI were as follows Boston Scientific: 1.9%, St Jude Medical: 10%, Medtronic: 50%. In multivariate analysis CRT-Ds reaching ERI had higher right ventricle lead output, left ventricle lead output and right ventricle pulse width (no values reported).

Results: published studies reporting complications due to replacement procedures

Lewis et al. (2016) conducted a systematic review to determine the risks and benefits of ICD generator replacement. A total of seventeen studies (n>167,000 patients) were included in the final systematic review. 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 e.g. incisional infection and pocket haematoma). The median rate for major complications was 4.05% (range: 0.55-7.37%). Infection requiring antibiotic therapy and/or extraction was the most frequently reported major complication with a median rate of 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%) and 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 to determine risk factors associated with cardiac implantable electronic device (CIED) infection. Their systematic review identified sixty studies which were relevant to their scope with a total of 233,184 patients. The average reported device infection rate for included prospective studies was 1.6% (n=21 studies), 1% for included case-control studies (n=9 studies) and 1.2% for included retrospective cohort studies (n=30 studies). Twenty studies reported the risk of infection associated with generator change (n=33,322 patients). The pooled odds ratio for device infection as a result of generator change 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 device 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”.

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, was carried out by Zeitler et al. (2015). The systematic review included seven studies which met the authors’ inclusion criteria with a total of 1,435 patients. This systematic review’s primary end-point was major complications while mortality and reoperation/pocket revision were considered to be “other” end-points. Major complications were defined differently by the authors of the included studies; however, for the most part major complications were defined as: death, any complication requiring reoperation (infection, bleeding/haematoma, system malfunction or pain) and any complication associated with device replacement. One included study focused on outcomes of device generator replacement in paediatric and congenital patients; the meta-analysis carried out by the authors excluded this study. Device generator replacement following US FDA recall was associated with a combined major complication rate of 2.60% (95% CI [0.9-4.8%]). Five out of the seven included studies reported the rate of death following the replacement of device generators; meta-analysis of this outcome gave a mortality rate of 0.4% (95% CI [0.1-1.1%]). Additionally, five out of the seven included studies reported the rate of reoperation/pocket revision; meta-analysis of this outcome gave a rate of 2.7% (95% CI [0.8-5.1%]). The authors conclude that generator replacement in response to a recall from the US FDA has a similar rate of major complications as elective generator replacement. Additionally, the authors 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). In their study 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 generator replacements and 2,063 (5%) CRT-D generator replacements. Lead damage was observed in 406 patients (0.90%) at a median of 107 days following generator 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, where patient demographic and clinical characteristics were controlled for, 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 and a median length of stay for lead damage was 3 days; this did not significantly differ based on the device type. The mean cost of lead damage management across the first year was $25,797; averaged across all device types. Lead damage management costs were significantly different across device types. Mean total hospitalisation costs were $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 of 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. Data is collected 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 generator 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 generator replacement. Lead performance in the 7458 patients undergoing generator replacement was compared to leads of similar age (68 months) in patients who did not undergo generator replacement. Patients who underwent generator 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, HR 1.02, 95% CI [0.98-0.99] ($p<0.001$) and HR 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 generator replacement. The authors suggest that surveillance is required following generator 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 generator replacement and 2.5% in lead age-matched controls ($p<0.001$).

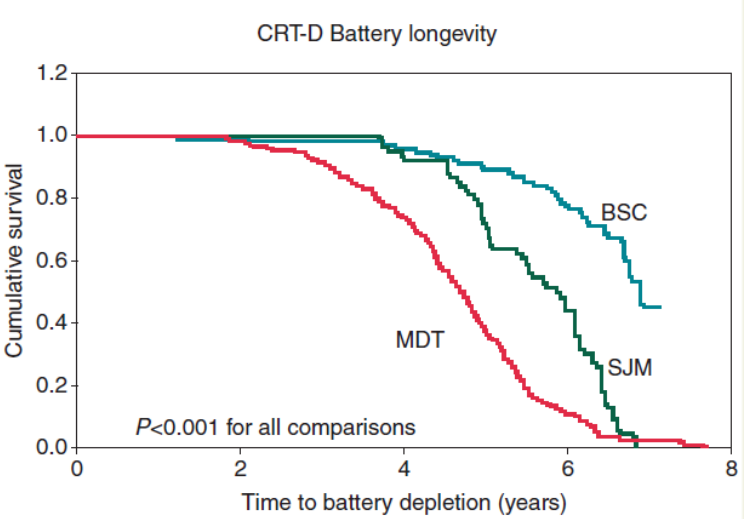
The results of the Danish cohort study [9] identified to the EAC by a clinical expert are shown in tables 11, 12 and 13.

Results: Product Performance Reviews

The company's submission provides the results of PPRs in Table B9 (page 65). These indicate:

- There is high variability in the selected follow-up points chosen across manufacturers for reporting of device longevity
- When device survival excludes normal battery depletion i.e. survival free from device malfunction only (where malfunction includes early battery depletion), device survival is high at practically all follow-up points: 94% and above. This means that device malfunctions are rare events.
- When device survival is considered as survival free from normal battery depletion plus malfunction: devices are observed to require replacement as time progresses i.e. normal battery depletion is by far the most common reason for explantation of a CRT-D.

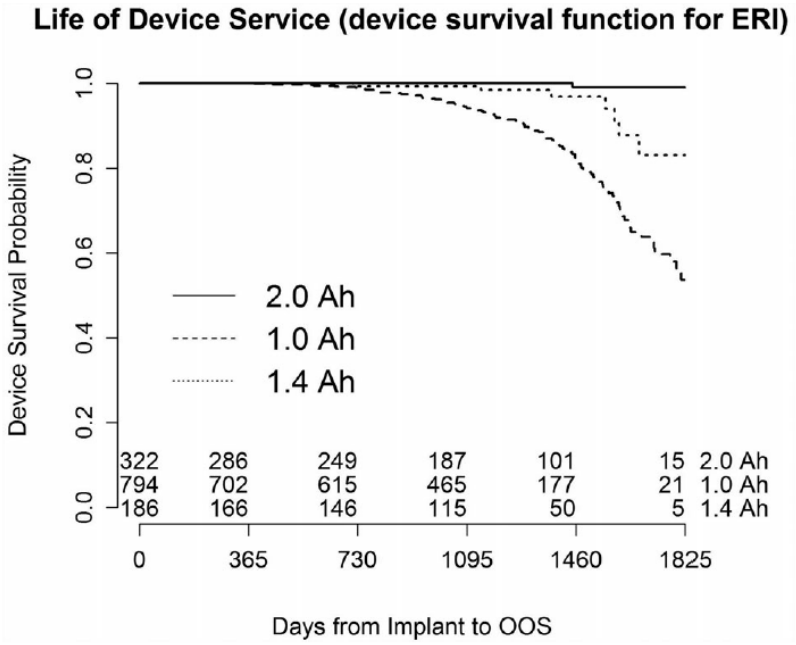
Table 4 Results of Alam 2016: published observational study reporting battery survival

Study	**Alam 2016** (an update of the same cohort reported as Alam 2014 shown below)
Follow-up	Mean 3.4 (SD ±2.1) years, median 3.7 (IQR 1.6, 5.0) years
Battery & device longevity	At mean follow-up 3.4 (SD 2.1) years: **Rates of replacement due to battery depletion (ERI):** Boston Scientific: 16% Medtronic: 51% St Jude Medical: 53% p < 0.001 **Time to battery depletion (unadjusted):** HR (SJM:MDT) 0.46 (95% CI 0.31, 0.68) p < 0.001 HR (BSC:MDT) 0.15 (95% CI 0.10,0.22) p < 0.001 HR (BSC:SJM) 0.28 (95% CI 0.16, 0.48) p < 0.001 **Time to battery depletion (adjusted for unbalanced electrical pacing parameters):** HR (SJM:MDT) 0.36 (95% CI 0.24, 0.54) p < 0.001 HR (BSC:MDT) 0.11 (95% CI 0.07,0.16) p < 0.001 HR (BSC:SJM) 0.25 (95% CI 0.13, 0.47) p < 0.001 **Kaplan-Meir analysis of CRT-D battery longevity**  BSC 173 119 83 39 MDT 391 271 160 18 SJM 57 43 43 10

<table>
<tr><td>Study</td><td>Alam 2016 (an update of the same cohort reported as Alam 2014 shown below)</td></tr>
<tr><td></td><td>
Percentage battery survival (%)by manufacturer: observations during follow-up versus PPR estimations
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr>
<tr><td colspan="7">Observed battery survival</td></tr>
<tr><td>Boston Scientific</td><td>100</td><td>98</td><td>98</td><td>95</td><td>90</td><td>77</td></tr>
<tr><td>Medtronic</td><td>100</td><td>99</td><td>92</td><td>74</td><td>36</td><td>10</td></tr>
<tr><td>St Jude Medical</td><td>100</td><td>100</td><td>100</td><td>90</td><td>69</td><td>44</td></tr>
<tr><td colspan="7">PPR estimated battery survival</td></tr>
<tr><td>Boston Scientific</td><td>100</td><td>100</td><td>100</td><td>99</td><td>98</td><td>98</td></tr>
<tr><td>Medtronic</td><td>100</td><td>98</td><td>93</td><td>81</td><td>62</td><td>34</td></tr>
<tr><td>St Jude Medical</td><td>100</td><td>99</td><td>98</td><td>95</td><td>87</td><td>66</td></tr>
<tr><td colspan="7">Absolute % difference</td></tr>
<tr><td>Boston Scientific</td><td>0</td><td>2</td><td>2</td><td>4</td><td>8</td><td>21</td></tr>
<tr><td>Medtronic</td><td>0</td><td>-1</td><td>1</td><td>7</td><td>26</td><td>24</td></tr>
<tr><td>St Jude Medical</td><td>0</td><td>-1</td><td>-2</td><td>5</td><td>18</td><td>22</td></tr>
</table>
For all manufacturers, PPR reports overestimated battery longevity, particularly beyond 4 years from device implantation.
</td></tr>
<tr><td>Factors associated with longevity</td><td>Not reported</td></tr>
<tr><td>CRT-D configuration</td><td>Not reported</td></tr>
<tr><td>EAC comments</td><td>Full journal article. 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) must represent a minor error. Of 173 Boston Scientific devices studied, 122 were powered by ENDURALIFE battery technology, so comparisons by manufacturer do not have complete applicability to the scope.</td></tr>
</table>

Table 5 Results of Ellis 2016: published observational study reporting battery survival

Study	**Ellis 2016**
Follow-up	Mean 3.0 (SD ±1.3) years (with no substantial difference between manufacturers)
Battery & device longevity	**Kaplan-Meier survival analysis: device survival function for battery depletion**



Device survival and out-of-service reason

	Overall	2.0 Ah (BSC)	1.4 Ah (SJM)	1.0 Ah (MDT)
Battery reached ERI	8.80%	0.30%	3.80%	13.50%
	115/1,302	1/322	7/186	107/794
Patient death	22.60%	28.00%	16.70%	21.80%
	294/1,302	90/322	31/186	173/794
Device revision	1.10%	0.60%	0.50%	1.40%
	14/1,302	2/322	1/186	11/794
Heart transplant	1.10%	1.60%	0.50%	1.00%
	14/1,302	5/322	1/186	8/794
CIED infection	1.20%	0.90%	0.50%	1.40%
	15/1,302	3/322	1/186	11/794
Other (device or lead failure)	2.30%	1.20%	1.60%	2.90%
	30/1,302	4/322	3/186	23/794

No device failures were observed in the study. The general pattern of devices reaching ERI by manufacturer were similar when analysed for low LV pacing output and high LV pacing output (defined as exceeding 3V@1.0ms).

Study	Ellis 2016

Factors associated with longevity

Univariate device parameters as predictor of ERI

	OR	95% CI	p
Ah by manufacturer (MDT 1.0 Ah vs BSC 2.0 Ah and SJM 1.4 Ah)	9.73	4.70, 20.15	<0.0001
LRL:			
<51 versus (51-61)	0.94	0.51, 1.72	0.8374
<51 versus (61-71)	0.62	0.33, 1.18	0.1426
<51 versus 71+	0.72	0.47, 1.11	0.1358
LV Impedance:			
>1,000 versus 500	0.38	0.20, 0.71	0.0025
>1,000 versus (500-700)	1.34	0.66, 2.73	0.4199
>1,000 versus (700-1,000)	0.71	0.35, 1.42	0.3275
BiV pacing:			
<70 versus (70-80)	0.5	0.04, 5.76	0.5782
<70 versus (80-90)	0.36	0.04, 3.1	0.3527
<70 versus (90-95)	0.31	0.04, 2.45	0.266
<70 versus (95-100)	0.43	0.08, 2.18	0.3067

Additional CRT-D programming predictors of ERI

	Overall	2.0 Ah	1.4 Ah	1.0 Ah	p
Presence of atrial fibrillation	40.20%	41.20%	45.20%	38.60%	0.252
	512/1,274	131/318	80/177	301/779	
LV threshold >3 V @ 1.0 ms	9.90%	13.80%	9.60%	8.30%	0.025
	123/1,246	43/312	17/177	63/757	
High shock/ATP burden* (>3 shocks)	19.30%	22.30%	10.50%	19.30%	0.288
	91/472	23/103	Apr-38	64/331	
BiV pacing percentage >95%	75.00%	61.50%	76.00%	80.30%	<0.001
	938/1,251	193/314	133/175	612/762	
85-95%	16.00%	27.10%	11.40%	12.50%	
	200/1,251	85/314	20/175	95/762	
<85%	9.00%	11.50%	12.60%	7.20%	
	113/1,251	36/314	22/175	55/762	
Atrial pacing percentage <25%	53.90%	62.00%	54.90%	50.20%	0.01
	570/1,058	168/271	84/153	318/634	
25-75%	28.50%	26.20%	27.50%	29.80%	
	302/1,058	71/271	42/153	189/634	
>75%	17.60%	11.80%	17.60%	20.00%	
	186/1,058	32/271	27/153	127/634	

Study: Ellis 2016

CRT-D configuration

Device parameters

Parameter	2.0 Ah (BSC)	1.0 Ah (MDT)	1.4 Ah (SJM)	Overall	p
LRL (low rate limit)	61.16 ± 8.90	62.38 ± 8.43	62.21 ± 7.26	62.05 ± 8.41	0.0902
LV impedance	715.88 ± 261.73	606.74 ± 269.51	662.75 ± 249.46	643.94 ± 268.01	0.0003
Atrial fibrillation at implant	41.20%	38.60%	45.20%	40.20%	0.1252
Atrial pacing %	27.32 ± 30.89	35.06 ± 33.63	33.10 ± 34.13	32.80 ± 33.16	0.0056
BiV pacing	92.83 ± 13.27	95.47 ± 12.44	93.59 ± 13.32	94.55 ± 12.82	0.0051

Programmed parameters

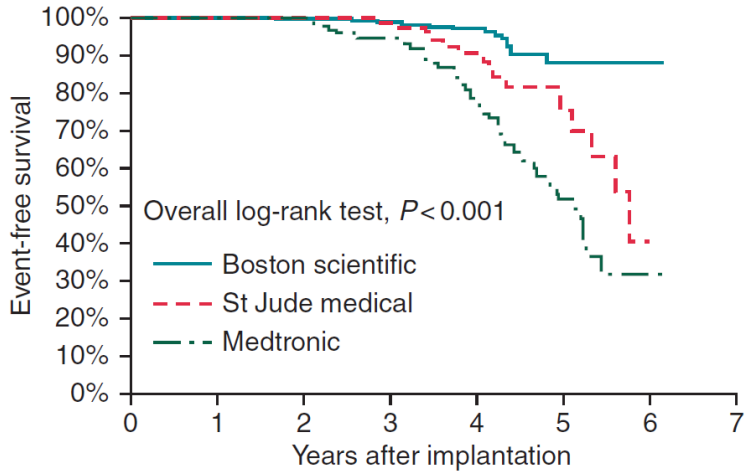
Parameter	Category	Overall	2.0 Ah (BSC)	1.4 Ah (SJM)	1.0 Ah (MDT)
RV lead programmed pacing voltage	Mean	2.24 ± 0.55	2.37 ± 0.5	2.23 ± 0.58	2.19 ± 0.55
	Median	2.08	2.33	2.08	2.01
	N	1,260	316	177	767
RA lead pacing voltage	Mean	2.07 ± 0.63	2.29 ± 0.55	2.12 ± 0.55	1.97 ± 0.66
	Median	2	2.21	2	1.86
	N	1,124	267	160	697
RA lead impedance (Ω)	Mean	486.2	528.8 ± 35.3	421.4	478.4
RV lead impedance (Ω)	Mean	516.6	551.7 ± 113.1	455.6	510.3

EAC comments: Full journal article. Authors report that the proportion of devices by manufacturer represents the market share distribution. No exclusions are reported. All device implant data were confirmed with manufacturers, including patients who transferred to long-term follow up at other centres.

Table 6 Results of Landolina 2015: published observational study reporting battery survival

<table>
<tr><td>Study</td><td>Landolina 2015</td></tr>
<tr><td>Follow-up</td><td>Median 43 months (IQR 18, 53) months i.e.3.6 (IQR 1.5, 4.4) years, 5201 person-years</td></tr>
<tr><td>Battery & device longevity</td><td>
Batteries still in service at 5 years follow-up in recent generation devices (marketed post 2007) and with n > 100:
Boston Scientific 88%
Medtronic 52%
St Jude Medical 75%
p<0.01

Kaplan-Meier analysis of device survival from replacement for battery depletion in recent generation devices (marketed post 2007) and with n > 100



<table>
<tr><td>Boston S.</td><td>291</td><td>234</td><td>205</td><td>187</td><td>144</td><td>27</td><td>1</td><td>0</td></tr>
<tr><td>St Jude M.</td><td>106</td><td>79</td><td>72</td><td>66</td><td>48</td><td>13</td><td>2</td><td>0</td></tr>
<tr><td>Medtronic</td><td>532</td><td>429</td><td>367</td><td>298</td><td>176</td><td>30</td><td>2</td><td>0</td></tr>
</table>
Number of patients with reported events

<table>
<tr><th>Manufacturer</th><th>n</th><th>Median follow-up (IQR)</th><th>All-cause replacement (%)</th><th>Battery depletion (%)</th><th>Deaths n (%)</th><th>Incomplete follow-up, n (%)</th></tr>
<tr><td>Biotronik</td><td>49</td><td>49 [34 - 56]</td><td>10 (20)</td><td>10 (20)</td><td>6 (12)</td><td>2 (4)</td></tr>
<tr><td>Boston Scientific</td><td>608</td><td>44 [16 - 55]</td><td>132 (22)</td><td>109 (18)</td><td>112 (18)</td><td>56 (9)</td></tr>
<tr><td>Medtronic</td><td>798</td><td>41 [18 - 52]</td><td>274 (34)</td><td>228 (29)</td><td>115 (14)</td><td>64 (8)</td></tr>
<tr><td>Sorin</td><td>99</td><td>47 [18 - 54]</td><td>22 (22)</td><td>20 (20)</td><td>14 (14)</td><td>8 (8)</td></tr>
<tr><td>St Jude Medical</td><td>172</td><td>44 [18 - 55]</td><td>41 (24)</td><td>34 (20)</td><td>27 (16)</td><td>16 (9)</td></tr>
</table>
40 CRT-Ds were removed due to device-related infection, 7 were removed at the time of heart transplant. 31 generators were replaced at the time of lead failure or elective replacement of a non-malfunctioning safety advisory lead.

For each manufacturer (except Biotronic, smallest group) newer generation devices had longer survival from replacement due to battery depletion, p<0.002.
</td></tr>
</table>

Study	Landolina 2015

Factors associated with longevity

Factors associated with replacement due to battery depletion

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Biotronik	0.75	0.40 - 1.41	0.369	-	-	-
Boston Scientific	0.54	0.43 - 0.67	0.001	0.64	0.47 - 0.89	0.008
Medtronic	1	-	-	1	-	-
Sorin	0.83	0.53 - 1.30	0.415	-	-	-
St Jude Medical	0.74	0.52 - 1.05	0.089	-	-	-
Recent generation	0.5	0.40 - 0.61	0.001	0.57	0.45 - 0.72	0.001
Battery chemistry: Li/SVO	1	-	-	1	-	-
Battery chemistry: Li/CFx-SVO	0.42	0.24 - 0.72	0.002	0.28	0.16 - 0.50	0.001
Battery chemistry: Li/MnO_2	0.2	0.13 - 0.33	0.001	0.37	0.22 - 0.64	0.001
High right atrial lead output*	0.7	0.39 - 1.24	0.219	-	-	-
High right ventricular lead output*	1.38	0.83 - 2.31	0.217	-	-	-
High left ventricular lead output*	1.74	1.39 - 2.18	0.001	1.96	1.57 - 2.46	0.001
Unipolar left ventricular lead	1.71	1.37 - 2.13	0.001	1.58	1.25 - 2.01	0.001
True-bipolar right ventricular lead	1.47	1.21 - 1.79	0.001	1	0.78 - 1.30	0.978
Percentage of biventricular pacing	1.2	0.91 - 1.58	0.207	-	-	-
Shocks delivered	1.58	0.59 - 4.20	0.365	-	-	-

Li/MnO2 Lithium manganese oxide
Li/SVO lithium silver-vanadium oxide
Li/CFx-SVO lithium silver-vanadium oxide and carbon monofluoride
* defined as pulse amplitude > 2.5 V and duration > 0.5 ms

In multivariate analysis of recent generation devices only, independent predictors of battery depletion were LV lead output (HR 3.09, 95% CI 2.18-4.38, p<0.001) and Boston Scientific CRT-Ds (HR 0.13, 95% CI 0.04-0.40, p<0.001).

CRT-D configuration

Pacing output, % biventricular pacing and total number of shocks delivered

	Biotronic	Boston Scientific	Medtronic	Sorin	St Jude Medical
Patients with high‡ RA lead output (%)	0		6	4	1
Patients with high RV lead output (%)	2	5	4	1	5
Patients with high LV lead output (%)	13	31*	18	31*	26*
% of patients with biventricular pacing <90%/90-95%/≥95%	10/13/77	12/10/77	9/14/76	16/18/65	11/13/75
% of patients with shocks delivered 0/1-10/10-20/>20	64/36/0/0	69/29/1/1*	85/13/0/1	83/17/0/0	74/26/0/0*

Study	Landolina 2015
	ǂ defined as pulse amplitude > 2.5 V and duration > 0.5 ms * p < 0.05 vs Medtronic The proportion of patients with LV pulse amplitude < 2.5 V and duration < 0.5 ms was higher in the Medtronic group (p<0.05) and Medtronic patients were less likely to receive a shock.
EAC comments	Full journal article. Of 608 patients in the Boston scientific group 291 had the Cognis CRT-D i.e. 48% were powered by ENDURALIFE battery technology. Paper does not report patient demographic and cardiac disease data. Although only 48% of BSC CRT-Ds were ENDURALIFE-powered CRT-Ds, the analysis of recent generation devices (marketed 2007 onwards) appears to include only 29 Livian CRT-Ds, suggesting that 291/320 = 91% of recent generation BSC CRT-Ds were ENDURALIFE-powered CRT-Ds.

Table 7 Results of Lau 2015: observational study reporting battery survival (abstract)

Study	**Lau 2015**
Follow-up	6 years
Battery & device longevity	Boston scientific devices had 100% survival from ERI at 6 years. St Jude Medical devices began to reach ERI after 2.8 years and Medtronic after 2.5 years **Pairwise comparisons of time to ERI:** Boston Scientific versus St Jude Medical: p = 0.0018 Boston Scientific versus Medtronic: p < 0.0001 St Jude Medical versus Medtronic: p = 0.00386
Factors associated with longevity	Not reported
CRT-D configuration	Not reported
EAC comments	Study available as abstract only: many details not reported, including patient factors, number of subjects per group and average follow-up. Non ERI events removing devices from service were censored.

Table 8 Results of von Gunten 2015: published observational study reporting battery survival

<table>
<tr><td>Study</td><td>von Gunten 2015</td></tr>
<tr><td>Follow-up</td><td>Median 53 (IQR 24-87) months i.e. median 4.4 (IQR 2-7.3) years</td></tr>
<tr><td>Battery & device longevity</td><td>
CRT-D devices by manufacturer & replacements
<table>
<tr><td></td><td>n (implanted)</td><td>n (replaced)</td><td>% replaced</td></tr>
<tr><td>Biotronic</td><td>228</td><td>23</td><td>10.1%</td></tr>
<tr><td>Boston Scientific</td><td>259</td><td>80</td><td>30.8%</td></tr>
<tr><td>Intermedics</td><td>0</td><td>0</td><td>0%</td></tr>
<tr><td>Medtronic</td><td>267</td><td>97</td><td>36.3%</td></tr>
<tr><td>St Jude Medical</td><td>526</td><td>116</td><td>22.1%</td></tr>
<tr><td>Sorin ELA</td><td>4</td><td>0</td><td>0%</td></tr>
<tr><td>Cameron</td><td>0</td><td>0</td><td>0%</td></tr>
<tr><td>Total</td><td>1284</td><td>316</td><td>24.6%</td></tr>
</table>
Survival of CRT-D devices (%)
<table>
<tr><td></td><td colspan="2">Implanted pre-2006</td><td colspan="2">Implanted 2006 onwards</td></tr>
<tr><td></td><td>5 year longevity (%)</td><td>6 year longevity (%)</td><td>5 year longevity (%)</td><td>6 year longevity (%)</td></tr>
<tr><td>Biotronic</td><td>0</td><td>0</td><td>76.2</td><td>44.9</td></tr>
<tr><td>Boston Scientific</td><td>43.5</td><td>17.5</td><td>97.6</td><td>97.6</td></tr>
<tr><td>Medtronic</td><td>39.2</td><td>7.4</td><td>74.1</td><td>46.3</td></tr>
<tr><td>St Jude Medical</td><td>61.5</td><td>30.9</td><td>45.3</td><td>26.5</td></tr>
<tr><td>All manufacturers</td><td>47.1</td><td>21.2</td><td>66.3</td><td>43.0</td></tr>
</table>
In 76 ENDURALIFE-powered COGNIS CRT-Ds there was 1 replacement representing 97.5% longevity at 4 years following implantation.
</td></tr>
</table>

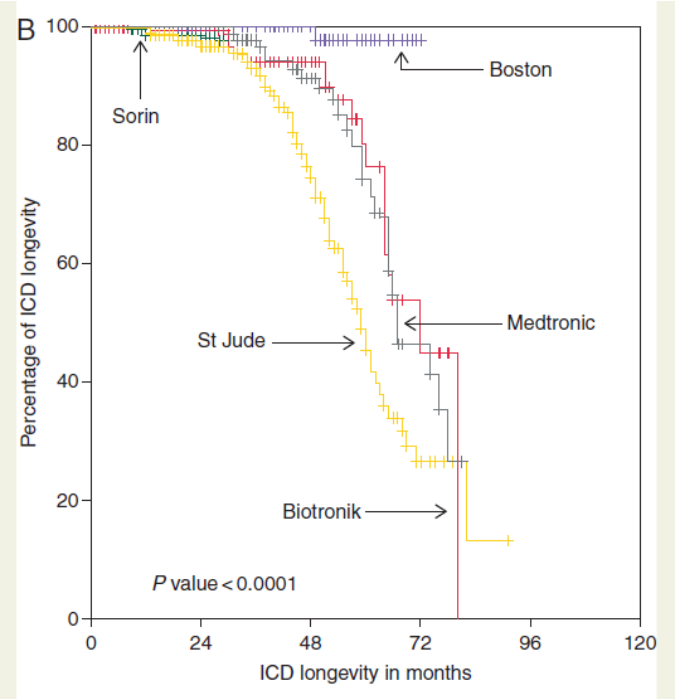
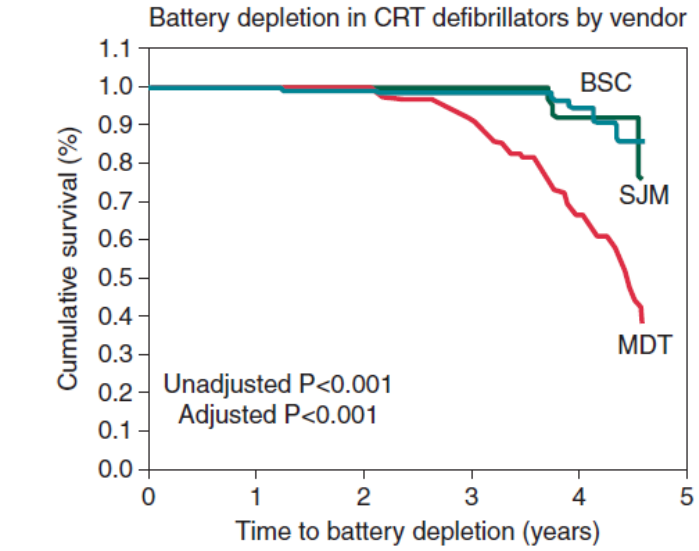
Study	von Gunten 2015
	Kaplan-Meier analysis of CRT-D longevity: 887 CRT-Ds implanted from year 2006 onwards  **Patient overall survival (all manufacturers & all ICD types):** 4-year 83.3% 5-year 80.1% 10-year 59.1%
Factors associated with longevity	Not reported
CRT-D configuration	Not reported
EAC comments	Full journal article. The paper reports on ICDs for out of scope patient indications including VVIs and DDDs in addition to CRT-D. The paper reports baseline characteristics (demographic, cardiac 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.

Table 9 Results of Alam 2014: published observational study reporting battery survival

Study	Alam 2014
Follow-up	**Median (IQR):** Overall: 3.1 (1.3-3.9) Boston Scientific: 3.0 (0.9-3.9) Medtronic: 3.1 (1.5-4.0) St Jude Medical: 3.2 (1.6-4.1)
Battery & device longevity	At overall mean follow-up of 2.7 (SD ±1.5) years: Of 122 ENDURALIFE-powered devices, 2 (1.6%) reached ERI and were replaced. **Devices that were replaced due to reaching ERI** Boston Scientific: 7/173 = 4% [ENDURALIFE-powered: 2/122 = 1.6%] Medtronic: 102/416 = 25% St Jude Medical: 4/57 = 7% p<0.0001 **4-year CRT-D device survival rate** Boston Scientific: 94% Medtronic: 67% St Jude Medical: 92% p<0.001 **Kaplan-Meier survival analysis of CRT-D battery depletion**  Boston scientific 172 128 113 87 34 Medtronic 415 333 287 216 100 St. Jude medical 56 45 39 31 15

Study

Alam 2014

Factors associated with longevity

Predictors of reaching ERI (adjusted for pacing burden, lead parameters in each chamber except for LV lead output and burden of ICD therapy)

	OR (95% CI)	p
Manufacturer*	6.27 (2.53, 15.52)	<0.001
RA impedance	1.00 (1.00, 1.00)	0.762
RV impedance	1.00 (0.99, 1.00)	0.786
LV output	1.97 (1.64, 2.37)	<0.001
LV impedance	1.00 (0.99, 1.00)	0.036
Proportion of patients receiving shock	1.29 (0.85, 1.95)	0.22

* Medtronic versus others

Patients whose batteries reached ERI had higher LV output (3.1+ 1.2 vs. 2.7+0.9 V, p < 0.001) and higher LV pulse width (0.8+0.4 vs. 0.6+0.3 ms, p < 0.001) compared with those who did not reach ERI. No other parameters were different between the devices reaching vs. not reaching ERI. This finding was present across all manufacturer groups.

CRT-D configuration

Device parameters

	Boston Scientific	Medtronic	St Jude Medical
RA output (V)	2.6±0.7	2.6±0.9	2.6±0.6
RA pulse width (ms)	0.49±0.04	0.49±0.11	0.50±0.14
RA impedance (Ω)*	493±195	604±596	396±67
RA pacing burden (%)	21±33	25±34	20±29
RV output (V)	2.8±0.7	2.6±0.8	2.8±0.7
RV pulse width (ms)	0.50±0.04	0.52±0.21	0.53±0.12
RV impedance (Ω)*	511±116	503±181	446±93
RV pacing burden (%)	91±17	92±20	94±16
LV output (V)*	2.9±0.9	2.7±1.0	2.7±0.8
LV pulse width (ms)	0.69±0.34	0.65±0.31	0.75±0.38
LV impedance (Ω)*	663±243	587±287	565±190
LV pacing burden (%)	94±12	92±20	94±14
Proportion of patients receiving any shocks including DFT testing (%)*	55	39	5.3
Proportion of patients receiving anti-tachycardia pacing (%)*	30	16	11

Patients implanted with Boston Scientific devices had highest programmed LV outputs and were most likely to receive device therapy.

EAC comments

Full journal article. Data suggest that all devices reaching ERI were replaced due to battery depletion. Of 173 Boston Scientific devices studied, 122 were powered by ENDURALIFE battery technology, so comparisons by manufacturer do not have complete applicability to the scope.

Table 10 Results of Williams 2014: observational study reporting battery survival (abstract)

<table>
<tr><td>Study</td><td>Williams 2014 (abstract)</td></tr>
<tr><td>Follow-up</td><td>Reported as 4 ± 0.8 years</td></tr>
<tr><td>Battery & device longevity</td><td>During 4 ± 0 8 years follow-up, 16 devices reached ERI (17 6%); CRT-Ds reaching ERI by manufacturer:

BSC 1 / 53 (1 9%)
MDT 14 / 28 (50%)
SJM 1 / 10 (10%)
(p < 0 001).</td></tr>
<tr><td>Factors associated with longevity</td><td>BSC had the highest RA lead impedance while MDT had the highest RV lead impedance (*p<0 05,
1-way ANOVA) Covariates that can affect time to battery depletion were included in a multivariate Cox proportional hazard model; Patients reaching ERI had higher RV and LV output and RV pulse width (values not reported).</td></tr>
<tr><td>CRT-D configuration</td><td>
<table>
<tr><th></th><th>BSC</th><th>MDT</th><th>SJM</th></tr>
<tr><td>RA Output (V)</td><td>2.2 ± 0.4</td><td>2.1 ± 1.1</td><td>2.3 ± 0.4</td></tr>
<tr><td>RA Pulse Width (ms)</td><td>0.52 ± 0.08</td><td>0.45 ± 0.19</td><td>0.53 ± 0.09</td></tr>
<tr><td>RA Impedance (Ohms)*</td><td>516 ± 109</td><td>476 ± 0</td><td>400 ± 47</td></tr>
<tr><td>RA Pacing (%)</td><td>27 ± 37</td><td>27 ± 31</td><td>55 ± 28</td></tr>
<tr><td>RV Output (V)</td><td>2.3 ± 0.5</td><td>2.4 ± 0.7</td><td>2.4 ± 0.3</td></tr>
<tr><td>RV Pulse Width (ms)</td><td>0.50 ± 0.10</td><td>0.54 ± 0.15</td><td>0.50 ±</td></tr>
<tr><td>RV Impedance (Ohms)*</td><td>509 ± 158</td><td>549 ± 188</td><td>397 ± 73</td></tr>
<tr><td>LV Output (V)</td><td>2.3 ± 0.8</td><td>2.2 ± 1.4</td><td>2.4 ± 0.7</td></tr>
<tr><td>LV Pulse Width (ms)</td><td>0.76 ± 0.32</td><td>0.77 ± 0.44</td><td>0.75 ± 0.35</td></tr>
<tr><td>LV Impedance (Ohms)</td><td>650 ± 198</td><td>685 ± 488</td><td>581 ± 273</td></tr>
<tr><td>BiV Pacing (%)</td><td>98 ± 2</td><td>91 ± 27</td><td>96 ± 5</td></tr>
<tr><td>Shocks per Patient</td><td>1.5 ± 2</td><td>1.2 ± 0.9</td><td>1.3 ± 0.5</td></tr>
</table>
* p < 0.05
</td></tr>
<tr><td>EAC comments</td><td>Study available in abstract only: full details not reported, including values for some outcome data.</td></tr>
</table>

Table 11 Number of complications based on CIED type and procedure type from Danish cohort study [9]

	Total (n=5918)	No complications (n=5356)	Complication (n=562)
CIED type			
Single-chamber PM	1160 (20%)	1080 (20%)	80 (14%)
Dual-chamber PM	3029 (51%)	2758 (52%)	271 (48%)
CRT-P	209 (4%)	189 (4%)	20 (4%)
Single-chamber ICD	684 (12%)	627 (12%)	57 (10%)
Dual-chamber ICD	391 (7%)	336 (6%)	55 (10%)
CRT-D	445 (8%)	366 (7%)	79 (14%)
Procedure type			
New implant	4355 (74%)	3923 (73%)	432 (77%)
Generator replacement	1136 (19%)	1069 (20%)	67 (12%)
System upgrade or lead revision	427 (7%)	364 (7%)	63 (11%)

Table 12. Cumulative incidence of complications at 6 months from Danish cohort study [9]

	All (n=5918)	New implant (n=4355)	Generator replacement (n=1136)	Upgrade/lead revision (n=427)
Any complication	562 (9.5; 8.7–10.2)	432 (9.9; 9.0–10.8)	67 (5.9; 4.5–7.3)	63 (14.8; 11.4–18.1)
Any major complication	329 (5.6; 5.0–6.1)	253 (5.8; 5.1–6.5)	40 (3.5; 2.4–4.6)	36 (8.4; 5.8–11.1)
Any minor complication	250 (4.2; 3.7–4.7)	189 (4.3; 3.7–4.9)	30 (2.6; 1.7–3.6)	31 (7.3; 4.8–9.7)
Major complications				
Lead related re-intervention	143 (2.4; 2.0–2.8)	120 (2.8; 2.3–3.2)	10 (0.9; 0.3–1.4)	13 (3.0; 1.4–4.7)
Infection	49 (0.8; 0.6–1.1)	24 (0.6; 0.3–0.8)	17 (1.5; 0.8–2.2)	8 (1.9; 0.6–3.2)
Local infection	22 (0.4; 0.2–0.5)	10 (0.2; 0.1–0.4)	8 (0.7; 0.2–1.1)	4 (1.0; 0.0–1.9)
Systemic infection/endocarditis	27 (0.5; 0.3–0.6)	14 (0.3; 0.2–0.5)	9 (0.8; 0.3–1.3)	4 (0.9; 0.0–1.9)
Pneumothorax requiring drainage	51 (0.9; 0.6–1.1)	45 (1.0; 0.7–1.3)	0	6 (1.4; 0.3–2.5)
Cardiac perforation	38 (0.6; 0.4–0.8)	35 (0.8; 0.5–1.1)	0	3 (0.7; 0.0–1.5)
No intervention	21 (0.4; 0.2–0.5)	18 (0.4; 0.2–0.6)	0	3 (0.7; 0.0–1.5)
Intervention[b]	17 (0.3; 0.2–0.4)	17 (0.4; 0.2–0.6)	0	0
Pocket revision because of pain	25 (0.4; 0.3–0.6)	10 (0.2; 0.1–0.4)	9 (0.8; 0.3–1.3)	6 (1.4; 0.3–2.5)
Generator-lead interface problem with re-intervention	7 (0.1; 0.0–0.2)	3 (0.1; 0.0–0.1)	4 (0.4; 0.0–0.7)	0
Haematoma requiring re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	1 (0.1; 0.0–0.3)	0
Other[c]	16 (0.3; 0.1–0.4)	16 (0.4; 0.2–0.5)	0	0
Minor complications				
Haematoma[d]	138 (2.3; 1.9–	104 (2.4; 1.9–2.8)	20 (1.8; 1.0–2.5)	14 (3.3; 1.6–5.0)

	2.7)			
Wound infection treated with antibiotics	69 (1.2; 0.9–1.4)	47 (1.1; 0.8–1.4)	12 (1.0; 0.5–1.7)	10 (2.3; 0.9–3.8)
Pneumothorax conservatively treated	39 (0.7; 0.5–0.9)	32 (0.7; 0.5–1.0)	0	7 (1.6; 0.4–2.8)
Lead dislodgement without re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	0	1 (0.2; 0.0–0.7)
Mortality	327 (5.5%) [e]	-	-	-

[a] Reported as absolute frequencies and percentages with 95% CIs in parenthesis
[b] Lead revision, pericardiocentesis, or both.
[c] Deep venous thrombosis (n=8), Twiddler's syndrome (n=3), wound revision (n=3), stroke (n=1), myocardial infarction (n=1)
[d] Resulting in prolonged hospital stay, hospital re-admission, or additional out-patient visit.
[e] One death was possibly procedure-related. No other deaths were thought to be as a result of procedure-related causes.

Table 13 Predictors for complications from Danish cohort study [9]

	Any major complication			Any minor complication		
	Risk (%)	Adjusted risk ratio (aRR)[b] (95% CI)	P-value	Risk (%)	aRR[b] (95% CI)	P-value
Gender						
Male[a]	5.0	–	–	4	–	–
Female	6.5	1.4 (1.2–1.8)	0.001	4.6	1.2 (0.9–1.5)	0.22
Age group, years						
0–39	7.8	1.3 (0.7–2.2)	0.36	3	0.5 (0.2–1.5)	0.23
40–59	7.2	1.1 (0.8–1.5)	0.38	4.8	1.0 (0.7–1.5)	0.94
60–79[a]	6.3	–	–	4.4	–	–
≥80	3.7	0.6 (0.5–0.8)	0.001	3.9	1.0 (0.7–1.3)	0.81
Body mass index, kg/m^2						
Underweight (<18.5)	8.0	1.5 (0.8–2.5)	0.17	6.8	1.5 (0.8–2.8)	0.21
Normal (18.5–24.9)a	5.6	–	–	4.4	–	–
Overweight (25–29.9)	5.3	0.9 (0.7–1.2)	0.41	3.7	0.8 (0.6–1.1)	0.15
Obese (≥30)	5.2	0.8 (0.6–1.1)	0.13	4.6	0.9 (0.7–1.3)	0.7
Centre volume						
0–249	5.7	1.4 (0.9–2.0)	0.13	2.9	1.7 (0.9–3.1)	0.09
250–499	5.3	1.4 (1.0–2.0)	0.054	5.7	3.5 (2.2–5.4)	,0.001
500–749	6.4	1.2 (0.9–1.6)	0.19	5.2	2.1 (1.4–3.0)	,0.001
≥750[a]	5.0	–	–	2.4	–	–
CIED type						
Single-lead PM	3.3	0.7 (0.5–1.0)	0.03	3.7	0.9 (0.6–1.3)	0.66
Dual-chamber PMa	5.5	–	–	3.8	–	–
CRT-P	6.7	1.6 (0.9–2.8)	0.11	3.8	1.5 (0.7–3.1)	0.3
Single-chamber ICD	5.4	1.2 (0.8–1.8)	0.39	3.2	1.3 (0.8–2.3)	0.52
Dual-chamber ICD	6.7	1.4 (0.9–2.2)	0.15	7.7	2.8 (1.7–4.5)	,0.001
CRT-D	11.0	2.4 (1.6–3.5)	<0.001	7.4	2.8 (1.7–4.4)	,0.001
Procedure type						

New implant[a]	5.8	–	–	4.3	–	–
Generator replacement	3.5	0.6 (0.5–0.9)	0.01	2.6	0.6 (0.4–0.9)	0.02
Upgrade/lead revision	8.4	1.3 (0.9–1.8)	0.18	7.3	1.5 (1.0–2.3)	0.03
Operator volume						
0–49	7.7	2.0 (1.3–3.1)	0.002	6.6	1.9 (1.2–3.1)	0.01
50–99	5.7	1.3 (0.9–1.8)	0.11	3.2	0.8 (0.5–1.2)	0.24
100–149	5.8	1.4 (1.0–1.8)	0.03	4.8	1.1 (0.8–1.5)	0.71
≥150[a]	4.9	–	–	3.9	–	–
Procedure priority						
Elective[a]	5.5	–	–	4.3	–	–
Emergency, daytime	6.5	1.3 (0.8–2.0)	0.24	3.5	1.1 (0.6–2.0)	0.76
Emergency, out-of-hours	7.2	1.6 (1.0–2.7)	0.07	4.5	1.4 (0.7–2.7)	0.32

[a]Reference group.
[b]Adjusted for gender, age, body mass index, centre volume, CIED type, procedure type, procedure priority, and operator volume.

3.7 Description of the adverse events reported by the Company

The EAC identifies two considerations with regard to adverse events:

- Complications that may arise from replacement procedures for CRT-Ds. The most common reason for need for replacement is normal battery depletion [15-19]. These complications are discussed in Section 3.4 and Section 3.6.

- Adverse events that may arise at any time, simply because CRT-Ds are active implantable Class III medical devices.

For the first category, complications associated with repeat procedures, the company undertook a second literature search which identified a body of 19 relevant studies. These are discussed in Section 3.4 and Section 3.6.

For the second category, adverse events, the company undertook a search of the US FDA MAUDE database and the UK MHRA database. The company provides a comprehensive description of adverse events identified, cited below:

"8,226 adverse events reported for ENDURALIFE-powered CRT-D devices, of which 5,086 (62%) have been classified as device-related. The remainder are classified as non-device related adverse events relating to infection, erosion, migration or procedure-related complications. Battery or longevity issues account for 1,764 of the device-related adverse events (0.76% of all units sold worldwide). 1,492 have had Corrective Actions implemented or completed the Corrective and Preventive Action (CAPA) process with established thresholds for long term monitoring. Of the remaining, 213 were unconfirmed adverse events (no device returned for analysis) and 59 were not associated with a Pattern. Of the 1,764 battery or longevity adverse events, 1,333 can be attributed to a specific AVX Bypass Capacitor issue (subject to an advisory). Mitigations and Corrective Actions were implemented for CRT-Ds and ICDs of the COGNIS™, TELIGEN™, INCEPTA™, ENERGEN™, PUNCTUA™, AUTOGEN™, INOGEN™, DYNAGEN™ and ORIGEN™ families. To date, there have not been any identified failures related to this pattern for the more recent AUTOGEN, INOGEN, DYNAGEN or ORIGEN families."

EAC search for adverse events

The EAC undertook its own search for adverse events. In the US FDA MAUDE database the EAC used the advanced search function and searched for the following brand names from 2008 to date: "ENDURALIFE" or "COGNIS" or "ENERGEN" or "PUNCTUA" or "INCEPTA" or "AUTOGEN" or

"INOGEN" or "DYNAGEN" or "ORIGEN". This returned 2677 results as follows:

- "ENDURALIFE" = 0
- "COGNIS" >500*
- "ENERGEN" >500*
- "PUNCTUA" = 286
- "INCEPTA" >500*
- "AUTOGEN" = 171
- "INOGEN" >500*
- "DYNAGEN" = 224
- "ORIGEN" = 26

* The search facility displays a maximum of 500 records. Where the number of identified records exceeds 500, the user is urged to refine their search.

The EAC also searched the UK MHRA database using the following terms: "Boston Scientific" or "CRT-D" or "cardiac resynchronisation therapy" or "ENDURALIFE" or "COGNIS" or "ENERGEN" or "PUNCTUA" or "INCEPTA" or "AUTOGEN" or "INOGEN" or "DYNAGEN" or "ORIGEN".

This identified two Medical Device Alerts as follows:

- (Boston Scientific) Rapid battery depletion leads to risk of loss of therapy. (MDA/2014/039). Issued: 7 October 2014
- (Boston Scientific) specific models of defibrillators implanted subpectorally have a risk of loss of shock therapy, inappropriate shock therapy, loss of pacing therapy or loss of anti-tachycardia pacing. (MDA/2010/012). Issued: 10 February 2010

The first alert relates to Boston Scientific COGNIS CRT-Ds that had experienced an increased rate of premature battery depletion due to a problem with a low voltage (LV) capacitor. This affected an additional 885 UK patients to the previous total of approximately 1,000 UK patients identified in August 2013. The alert states that the manufacturer notified pacing clinics about the recent introduction of updated Safety Architecture software that will

improve early detection of the problem. The reported prevalence of failures was 2% at this report date.

The second alert, which also applies to the COGNIS CRT-D, describes risks for subpectoral implants of:

- loss of shock therapy
- inappropriate shock therapy
- loss of pacing therapy
- loss of anti-tachycardia pacing

The risk arises from physical damage to the CRT-D casing during implantation or subsequent force applied against the patient's rib cage. The manufacturer has confirmed two (non-UK) reports of device malfunction associated with this issue out of approximately 77,000 devices sold worldwide. Both devices required early replacement (at four and five months post-implant) as they had delivered inappropriate shocks. The manufacturer recommended actions to clinicians which included active identification of patients who may be affected, changes to programmed configurations in affected CRT-Ds, patient counselling and follow-up, avoidance of future subpectoral implantation and potentially, CRT-D replacement.

EAC conclusion on adverse events

The company identified over 8000 adverse events relating to ENDURALIFE-powered CRT-D devices, whereas the EAC identified 2677.

The company is likely to be highly vigilant for adverse events for all of the implantable devices that it markets, and has likely identified more adverse events than the EAC by its own active surveillance and close communication with regulatory bodies and clinical sites.

The EAC has not attempted to further categorise the large number of adverse events identified. The EAC considers that CRT-Ds are technologically advanced, active implantable, Class III medical devices with indications in patients at risk of serious morbid incident or mortality. Published evidence indicates that CRT-Ds improve patient survival [20], though due to their complex design and function, plus implantation in large numbers of patients globally, adverse events are to be expected across all manufacturers. High vigilance for adverse events is likely to be a feature of the entire CIED industry and the EAC is not aware of specific trends by which adverse events

related to CRT-Ds from any particular manufacturer are more likely than from other manufacturers.

One expert clinical advisor indicated support for our conclusions on adverse events.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the Company

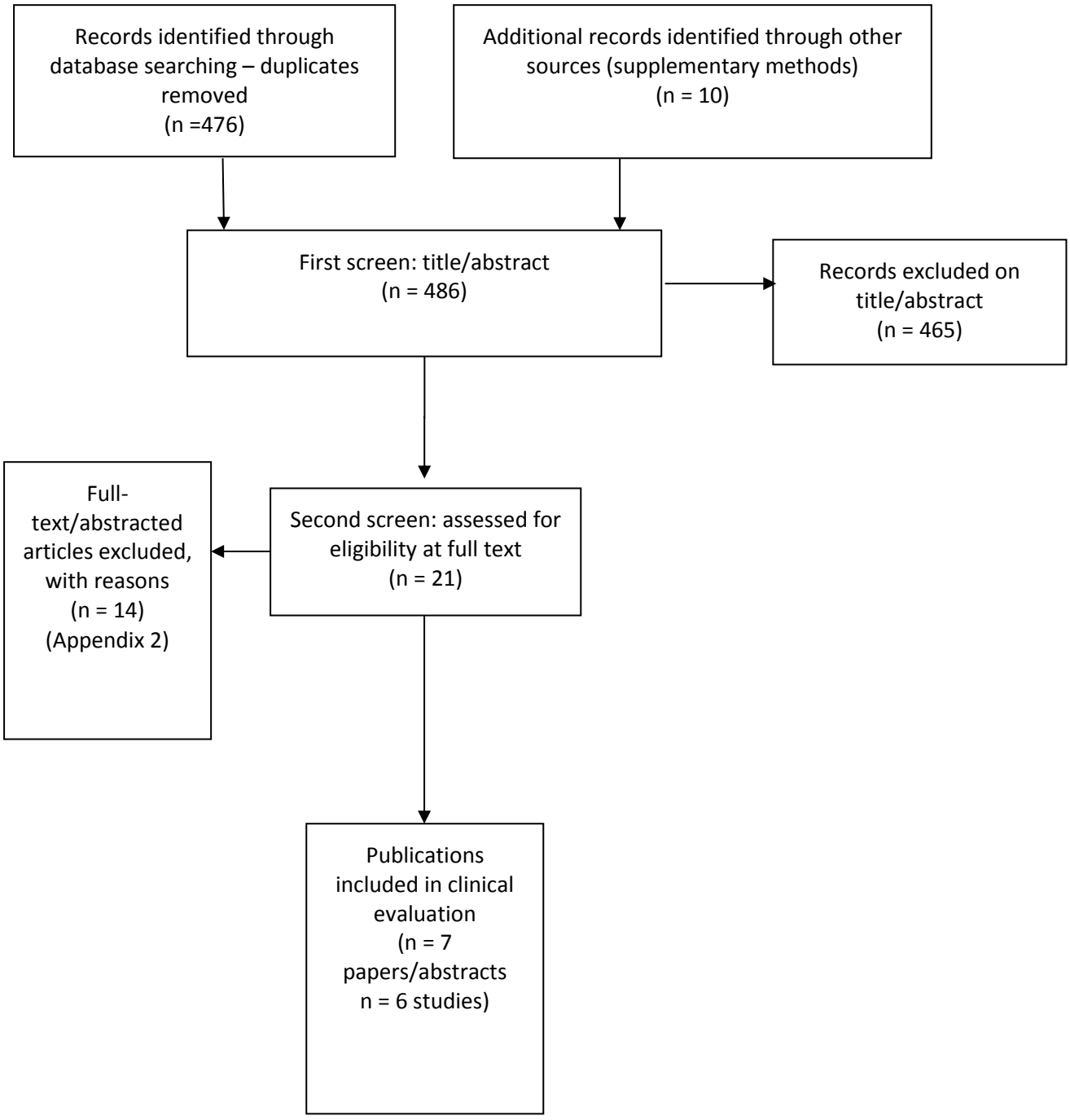
Neither the Company, nor the EAC, conducted evidence synthesis/meta-analysis.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

3.9.1 EAC literature search

The EAC devised their own searches for clinical and economic evidence in accordance to the NICE requirements for a Company's submission of evidence. The EAC designed one search for both clinical and economic evidence in each of following sources: Medline; Medline In-Process; Embase; The Cochrane Library and PubMed. The following additional sources were searched for economic evidence: Cost Effectiveness Analysis registry; EconPapers and EconLit. In addition the EAC searched the International Clinical Trials Registry Platform and Clinicaltrials.gov for ongoing studies and the MHRA for adverse events related to ENDURALIFE-powered CRT-D devices. Citation tracking of the Company's included studies for clinical evidence was performed in Web of Science and Scopus and the reference lists were checked for other relevant publications. The figure below shows the EAC's study selection process.

Figure: EAC study selection flow chart: published studies of CRT-D device longevity



3.10 Conclusions on the clinical evidence

The Company's submission of published studies of CRT-D longevity provide head-to head comparisons of ENDURALIFE-powered CRT-Ds with contemporary comparator CRT-Ds. A minority of these studies have limited applicability to the scope by including a large proportion of ICDs as opposed to CRT-Ds [6] and also by including devices installed well before the introduction of the ENDURALIFE battery technology in the year 2008.

The longevity studies have the strength that they were conducted in as near to normal clinical practice as possible, and in countries that are acceptably similar to the UK in terms of population and care pathway. However weaknesses include retrospective analysis, and that it is not possible to determine why study participants were implanted with a CRT-D from a particular manufacturer.

The published studies of longevity demonstrate that for the period of implantation studied since 2008, ENDURALIFE-powered CRT-Ds have better longevity than comparator CRT-Ds.

Some of the CRT-Ds studied in the longevity studies, particularly for comparator devices, may no longer be marketed.

The EAC considers that battery capacity is an important factor which may potentially determine CRT-D device longevity, but also that it does not act in isolation and that other CRT-D factors are also important (see Technical Assessment). It is likely that different manufacturers have each undertaken constant 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 published longevity studies. For this reason the EAC collected and examined data on predicted battery longevity for currently available CRT-Ds across manufacturers. However the EAC considers these data to have high uncertainty because they are derived from bench testing under conditions which differ across manufacturers. Therefore no further analyses were performed by the EAC using projected longevity data.

The EAC accepts the Company's submission of evidence on the rate of complications following replacement procedures for CRT-D. There is a degree of duplication whereby data from primary studies included by the company are also used in systematic reviews, also within the Company's submission. For this reason the EAC has focussed on systematic review data and other data from primary studies that are not duplicated.

The EAC observes that adverse events are likely to be frequent, considering that CRT-D is a class III implantable medical device, used in people with heart failure and potential comorbidities. Consequently the FDA MAUDE database records a high number of entries for CRT-Ds. The EAC has seen no evidence that ENDURALIFE-powered CRT-Ds present a particular risk of adverse events compared to comparator CRT-Ds, and adverse events in normal use are not included in the economic evaluation.

PPRs submitted by the Company demonstrate that, for the vast majority of implanted CRT-Ds, it is normal battery depletion that is the reason for CRT-D replacement, and not device malfunctions. Otherwise, due to limitations and variability across manufacturers in the methods behind PPRs, the EAC accepts that the published studies of longevity present more robust data on longevity than do the PPRs.

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The company's search was limited to three publically available databases: Pubmed, Cochrane and clinical trials.gov, supplemented by additional searching of company documentation. The search was limited to English language publications. The search did not include all of the databases specified in the submission template e.g. Medline, Embase, EconLit and NHS EED. The search criteria used are somewhat limited and the EAC conducted a more comprehensive search applied to more databases. The company's search was reasonable but could be improved with access to more databases and a more thorough strategy.

Critique of the company's study selection

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 'Patients undergoing CRT-D device implantation for heart failure in line with NICE Technology Appraisal 314'. The company's population is broader and probably reflects the lack of detail in the published evidence on the specific criteria used in TA314.

Included and excluded studies

The company included seven studies of which five were published and two full papers were academic in confidence. Three of the published studies were conference abstracts. The company did not rely on the published studies for its model, although the structure of the de novo model is similar to the model described in the Gadler draft publication [36].

The reason given by the company for excluding three of the studies was because of 'no direct correlation between longevity and costs described'. This reason was not part of the company's exclusion criteria. The EAC has obtained these papers and concluded that they are not relevant to the economic evaluation. One study was about leads rather than CRT-D devices

and the other two papers were not about manufacturer specific devices, but CRT-Ds in general. The EAC excluded 3 papers included by the company as they were outside the scope.

The Boriani 2013 paper [37] 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 2011 paper [38] 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 2015 abstract [39] 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.

Overview of methodologies of all included economic studies

Two of the abstracts are similar and compared costs for unspecified devices. Comparator device longevity was taken from ‘a recent NICE review’ and compared with longevity of devices from Boston’s Latitude patient management system. One abstract models costs for Australia [40] and the other for the UK [41]. The Latitude system is a telemonitoring system and longevity data from Latitude may not be directly comparable with data reported in the NICE review. The patient populations may be different. Much of the Latitude data may originate in the USA. Studies presented as abstracts lack sufficient descriptions of their methodology to enable thorough critique. Therefore the results from these abstracts should be treated with caution.

The unpublished Landolina 2016 manuscript [42] describes an economic analysis based on a subset of the data from Landolina 2015 [4] 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 [4], 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 XE currency converter €1 = £0.847 on 12/07/2016) with a maximum difference in cost of 40% for hospitals and 19% for the Italian healthcare system. The authors do not clearly specify which manufacturers supplied the least or most costly technologies over the 6 years.

The unpublished Gadler 2016 manuscript [36] describes [redacted]

Overview and critique of the Company's critical appraisal for each study

The company described the economic studies in Table C4 of the manufacturer submission and included a quality assessment for each study in Table C9, but there was no other critical appraisal of the studies.

Does the Company's review of economic evidence draw conclusions from the data available?

The company noted that all of its selected economic studies were based outside of the UK apart from the Duxbury 2014 abstract [41]. Duxbury did not report on the cost impact for CRT-D devices separately. Therefore the company concluded that a new model was required.

4.2 De novo cost analysis

Patients

The company states that the model population is as described in the scope i.e. it is in line with TA314. The clinical data used in the model are taken from the Landolina 2016 [42] economic study. This appears to be a sub-set of the same population as reported in Landolina 2015 [4].

Technology

The technology considered is CRT-D devices using ENDURALIFE battery technology, specifically (based on devices used in the Landolina 2015 study [4]):

Table 14 Battery characteristics: Boston Scientific

Manufacturer	Device	Year of CE mark	Battery chemistry	Battery capacity
Boston Scientific	Renewal	2004	Li/SVO	2.00Ah
Boston Scientific	Livian	2007	Li/CF_x-SVO	1.86Ah
Boston Scientific	Cognis	2008	Li/MnO_2	1.84Ah

Our understanding is that Cognis is an ENDURALIFE-powered CRT-D but that Livian and Renewal are not. Data in the model was taken from recent

generation technologies and this would be from Cognis devices for Boston Scientific.

Comparator(s)

The economic model includes as comparators the following devices (based on devices in the Landolina 2015 study [4]):

Table 15 Battery characteristics: comparator CRT-Ds

Manufacturer	Device	Year of CE mark	Battery chemistry	Battery capacity
Medtronic	InSync III Marquis	2003	Li/SVO	0.9Ah
Medtronic	InSync Sentry	2004	Li/SVO	0.89Ah
Medtronic	InSync Maximo	2005	Li/SVO	0.89Ah
Medtronic	Concerto	2006	Li/SVO	1.00Ah
Medtronic	Consulta	2008	Li/SVO	1.00Ah
Medtronic	Maximo II	2008	Li/SVO	1.00Ah
Medtronic	Protecta	2010	Li/SVO	1.00Ah
St Jude Medical	Atlas	2003	Li/SVO	NR
St Jude Medical	Epic	2006	Li/SVO	NR
St Jude Medical	Promote	2007	Li/SVO	NR

In Landolina 2015 [4] recent generation models were for the most part released from 2007 to 2010.

Model structure

The model is a decision tree with a 6 year time horizon and an NHS perspective. The implant is Boston Scientific (with ENDURALIFE battery

technology) as the intervention with comparators from Medtronic or St Jude Medical. 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.

Key assumptions in the model are:

- The 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.

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 we consider the problem from the viewpoint of the patient population and consider that 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 equal, then the only difference in cost would arise from discounting for costs incurred in the future. In the extremes, the impact of device longevity would be important, so a 2 year device lifespan would incur multiple replacements and if the lifespan were 20 years there would be no need for replacements. The choice of a 6 year time horizon potentially exaggerates the cost saving of a slightly longer lasting device.

Clinical parameters and variables

Clinical data in the model is taken from the Landolina 2016 draft manuscript [42] for event-free battery survival and Yao et. al. 2007 [21] for cumulative probability of patient survival. The incidence of complications is taken from Tang et. al. 2010 [20] 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).

The EAC scrutinised the Yao paper [20] and found that the data collected extends only up to about 2.5 years. Patient survival was modelled statistically by the authors up to 6 years and the company has manually extracted estimates of cumulative survival probability from the printed graph by eye. This is a rather imprecise method and in any case is based upon a model rather than actual survival data. Therefore there is some uncertainty regarding the values of cumulative probability of survival used in the model. The company's sensitivity analysis explored the probability of survival in a robust way and therefore the EAC did not pursue any further analysis.

The EAC contacted clinical experts to validate the incidence of complications used in the model.

Tele-monitoring

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 Consultant 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. 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.

Resource identification, measurement and valuation

The company has taken procedure costs from the payment by results (PbR) tariff and chose not to use NHS reference costs from 2014-15. 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. Therefore the EAC considers that NHS reference costs warrant exploration as a data source for the model.

Table 16 NHS costs

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

Substituting the NHS reference cost for de novo implantation £14,984 and for replacement £2,864 gives the results shown in Table 17 below.

Table 17 Results of model after substituting NHS reference 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%

Technology and comparators' costs

The company based the costs of technologies on the assumption that all of the devices cost the same. In the model, the device cost is a key driver and therefore this is a significant weakness of the model. A new centralised procurement list has been developed to drive out variation and secure better prices from suppliers and includes CRT-D. This tends to suggest that prices have been variable for these high cost devices. Therefore the EAC considers the sensitivity analysis needs to explore differences in the price of the technology compared with the comparators, and to identify thresholds at which the model becomes cost neutral.

Sensitivity analysis

The company undertook univariate sensitivity analysis. There was no multi-variate or probabilistic sensitivity analysis.

4.3 Results of de novo cost analysis

Table 18 Base-case analysis results

Technology	Ave cost/patient over 6 years	Difference	% Difference
ENDURALIFE-powered CRT-Ds	£22,322		
Medtronic CRT-Ds	£29,158	+ £6,836	+ 31%
St Jude Medical CRT-Ds	£27,309	+ £4,986	+ 22%

Sensitivity analysis results

The inputs for the sensitivity analysis are shown in Table C21 of the manufacturer's submission.

Table 19 Difference in cost per patient between Medtronic vs ENDURALIFE-powered CRT-Ds (Boston Scientific)

	MDT-BSC		
	Base	**Low**	**High**
MDT device costs	£6,836	£3,253	£10,420
MDT event-free battery survival	£6,836		£4,623
Warranty eligibility & uptake	£6,836		£4,910
Cumulative probability of patient survival	£6,836	£5,869	
Replacement procedure cost	£6,836	£6,475	£7,197
Incidence of complications	£6,836	£6,573	
Cost of complications	£6,836	£6,749	£6,923

Follow-up costs	£6,836	£6,829	£6,844
Initial procedure cost	£6,836	£6,836	£6,836
Frequency of routine follow-up appointments	£6,836	£6,836	£6,836

Table 20 Difference in cost between St Jude Medical vs ENDURALIFE-powered CRT-Ds (Boston Scientific)

	STJ-BSC		
	Base	**Low**	**High**
STJ device costs	£4,986	£1,649	£8,323
STJ event-free battery survival	£4,986		
Warranty uptake	£4,986		£4,400
Cumulative probability of patient survival	£4,986	£4,179	
Replacement procedure cost	£4,986	£4,512	£5,566
Incidence of complications	£4,986	£4,795	
Cost of complications	£4,986	£4,872	£5,126
Follow-up costs	£4,986	£4,977	£4,998
Initial procedure cost	£4,986	£4,986	£4,986
Frequency of routine follow-up appointments	£4,986	£4,986	£4,986

Sensitivity analysis: device survival

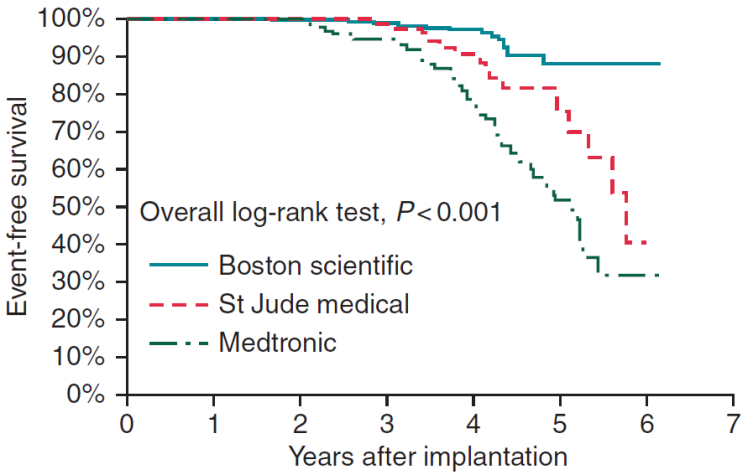
The base case analysis uses empirical data on device longevity from the unpublished Landolina (2016) study [42], where CRT-Ds were implanted in the interval January 2008-March 2010. In sensitivity analysis the company explored the effect of modelling the projected longevity of the latest

generation of CRT-Ds, marketed currently (year 2016). Projected longevity was taken from publicly available 'instructions for use' documents'. These documents provided useable projected longevity data only for Boston Scientific and Medtronic devices. The company calculated the average percentage improvement in longevity (time) between older devices and the contemporary devices (17% for Medtronic devices) and applied this percentage improvement to each time point in 0.2 year intervals. For Medtronic CRT-Ds, a given percentage of CRT-D survival would be reached 17% later: in effect, moving the Kaplan-Meier survival curve to the right and assuming that here is no change to the shape of the curve. The changes in input values to the model were as follows:

Table 21: modified CRT-D survival rates for company's sensitivity analysis

Year	Medtronic	
	Base case	Sensitivity analysis
0	100%	100%
1	100%	100%
2	99%	100%
3	92%	95%
4	78%	88%
5	50%	70%
6	30%	47%

Kaplan-Meier analysis of device survival from replacement for battery depletion in recent generation devices (marketed post 2007) and with n > 100 (Landolina, unpublished, 2016 [42]).



Boston S.	291	234	205	187	144	27	1	0
St Jude M.	106	79	72	66	48	13	2	0
Medtronic	532	429	367	298	176	30	2	0

The effect of the company's sensitivity analysis is to reduce the additional cost incurred by Medtronic devices over Boston Scientific devices from £6,836 to £4,623.

The EAC acknowledges that this is an attempt to apply the model to the latest available CRT-Ds, on a within manufacturer basis (assuming that each manufacturer applied the same methods to estimate projected longevity over time). However the EAC considers the following as important limitations:

- The projected longevity data are derived from bench testing and not from observed clinical use and are therefore subject to uncertainty.
- The sensitivity analysis was applied only to Medtronic CRT-Ds in the model because St Jude Medical documents do not state projected longevity.
- It is not certain that each manufacturer used the same methods to estimate projected longevity over time.

- It is unclear if the CRT-D device survival, of newer generation versus older generation devices from the same manufacturer, can be extrapolated in this way, i.e. that the survival curves shown above [4] would retain a similar shape.

Subgroup analysis

No sub-group analysis was included.

Model validation

The company did not approach clinical advisers to assess the applicability of clinical or resource inputs used in the model. They performed internal and external quality assurance to ensure the model performs as intended.

4.4 Interpretation of economic evidence

The company states that the results of the de novo model are consistent with the published economic literature. The two full *unpublished* papers from Gadler 2016 [36] and Landolina 2016 [42] [redacted] Boston Scientific provided funding for both of these economic studies.

Two abstracts [40, 41] demonstrated cost saving for longer lasting batteries using data from Boston Scientific's latitude patient management system when compared with unspecified 'industry standard' batteries taken from a market average from the recent NICE TA 314, based on the NICOR registry which includes all implants in the UK for a 10 year period. These studies had longer time horizons of 15 years [40] and 10 years [41]. The cost savings of switching from industry standard to increased longevity batteries in Priest

2015 [40] were, in Australian dollars, $9,313 (£5,318 1 AUD = £0.571, XE currency converter 15/07/16) per patient over 15 years. The results in Duxbury 2014 [41] were expressed as additional procedures that could be funded from the reduction in replacements. Both studies were co-authored by Boston Scientific.

The company has correctly identified the main limitation of the model, being the difference in device models in the published literature compared to those available now. They also note that the sample size at year 6 is small. The company investigated the effect of a price difference between the technology and the comparators by applying +/- 20% to the average selling price (based on all manufacturers in NICE TA314) for Medtronic CRT-Ds and for St Jude Medical CRT-Ds. The effects of these analyses on the model are small compared to the effects of using highest and lowest device list prices: purchase cost is a key driver of the model.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC obtained list prices for currently available CRT-D devices and ran the model with list prices in place of the average selling price.

List price analysis

The EAC obtained list price data from manufacturers and used these as model inputs.

Table 22 Manufacturer list prices

Make	Model	List price
Boston Scientific	[redacted]	[redacted]
St Jude Medical	[redacted]	[redacted]
	[redacted]	[redacted]

	[redacted]	[redacted]
Medtronic	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]		

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

[redacted]

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

The company has provided evidence that list prices do not reflect actual selling prices. This evidence is average selling prices collated by Eucomed based on quarterly sales data: each manufacturer receives both a generalised market average selling price plus their own specific average selling price. The EAC accepts that differences between list price and actual selling price exist. 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. Because device cost was identified as a key driver of the model, the EAC undertook threshold analysis as follows.

Threshold analysis of price difference between devices

The EAC investigated the effect of allowing a price difference between the devices and calculated the threshold at which the technology becomes cost saving compared with the comparators.

Table 25: Threshold implant costs

	Boston scientific	**Medtronic**	**St Jude Medical**
CRT-D implant cost	£12,404	£7,546	£8,546
CRT-D replacement cost	£11,858	£7,000	£8,000

Table 26 Model results 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 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.

Analysis using manufacturer warranty data

The EAC obtained data on the warranty period for currently available models of the comparator and used these values in the model. In the model, the company assumes that the warranty arrangements for the comparator technologies are the same as those for Boston Scientific i.e. full replacement cost up to 4 years and an additional 2 year pro rata warranty credit. In the base case it is assumed that warranty refunds are not claimed. In sensitivity analysis the option for 100% of refunds to be eligible and claimed within the warranty period is explored.

The EAC has obtained information on actual warranties for Medtronic and St Jude devices from the manufacturers and these are listed in Tables 27 and 28 below.

A clinical expert stated to the EAC that CRT-D warranties are comprehensive because CRT-D devices are robust, and that in reality warranties are very rarely claimed by clinical teams as process to do so in most hospitals are lacking.

Table 27 Warranty information supplied by St Jude Medical

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

[redacted]	[redacted]	[redacted]

Table 28 Warranty information supplied by Medtronic

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

[redacted]

[redacted] The results are given in Table 29.

Table 29 Results using warranty information from manufacturers

ENDURALIFE-powered CRT-Ds	£22,322		
Medtronic CRT-Ds	£23,644	+£2,279	+11%
St Jude Medical CRT-Ds	£23,027	+£1,663	+8%

Complications

The company's rates of different kinds of complications used in the model were taken from a randomised study comparing de novo ICD versus de novo CRT-D in people with heart failure, and were the same rates as used by NICE in their technology appraisal 314. Complications were reported for the 30 day period following de novo implantation of CRT-D devices [20] . Rates of complications used as inputs to the model were infection: 2.4%, lead dislodgment or haematoma requiring re-intervention: 8.5%, and device-pocket problem requiring revision: 0.5%, with rates assumed to be equal for de novo and replacement procedures. The EAC considered that rates of complications may differ between de novo implant and replacement procedures. The EAC consulted clinical experts, one of whom highlighted that the best available data on complications following replacement of cardiac implantable electronic devices (CIEDs) comes from a cohort study conducted in Denmark [9]. This study reported complications following 4335 de novo implantations and 1136 replacement procedures for CIEDs: the data are not disaggregated for

different types of CIED, but the EAC considers that this is a lesser limitation than assuming that de novo and replacement procedures have equal rates of complications.

Clinical experts also reported their experience of complications to the EAC as follows:

Clinical expert 1

- de novo implants have complication rates 8-10% with an infection rate of 0.6-1%
- Replacements have similar complication rates but higher infection rate (2-2.5%)
- Infections are likely under-reported, can lead to complicated extractions and require implantation of a new CRT-D and leads on the contralateral side.

Clinical expert 2

- Frequently quoted rates of infection are around 2%
- The rate of complications requiring re-intervention (lead dislodgement, haematoma) of 8.5% is much higher than would be expected at box-change. Haematoma requiring re-intervention should be <0.5% and lead displacement should be <1%.
- The rate of device pocket problem requiring revision of 0.5% is lower than conventionally quoted and is inconsistent with the infection point as infection is a sub-set of pocket problems requiring re-intervention.

The EAC considered that the company's sensitivity analysis covered the majority of the discussion above and also the range of different complications reported in the cohort study [9]. An exception is that the cohort study found the rate of infection in new implants to be 0.6% (24/4355). The EAC inputted this rate of infections for new implants in the model: the effect is very small as shown in Table 30: the effect on the model is negligible: a 1% percentage increase in excess cost for St Jude Medical CRT-Ds.

Table 30 Effect of changing the rate of infection (new implants) from 2.4% to 0.6%

[redacted]	**Total cost**	**Excess cost over BSC**	**% excess cost over BSC**
[redacted]	£22,322		
[redacted]	£29,158	+ £6,836	[redacted]
[redacted]	£27,309	+ £4,986	[redacted]

The EAC conclusion on rates of complications used in the model is that they are broadly appropriate, with variations adequately explored in sensitivity analysis.

Analysis using manufacturer projected longevity

The EAC hoped to develop some scenarios based upon the projected battery lifespan as estimated by the manufacturers or from PPR reports for currently available models of the technology and comparators. However the EAC concluded this was not a valid approach because:

Bench test data:

- Settings may not reflect clinical realities
- Different manufacturers choose to report different settings, and therefore results are not comparable
- Single figure given for longevity, rather than a graph of survival against time

PPR data:

- Data is usually collected passively, resulting in under-reporting of malfunctions
- Assumption that devices are still functioning unless they are returned, or the manufacturer notified

- Data can only show device survival for the length of time that the device has been implanted
- Patients and settings may be different for different devices, this may be a systematic difference due to different device capabilities or functions.
- By the time a complete longevity curve is available the device is likely to have been superseded.

The model uses a year by year survival curve to represent device longevity based on data from Landolina 2016 [42]. Manufacturer's projected longevity is a point estimate. Calculating projected device longevity is complex and there is no agreed standard approach. Each manufacturer makes its own assumptions in its calculation. Therefore the estimates of projected longevity are not directly comparable from a technical viewpoint, and incorporating the data into the model would require further assumptions regarding the survival curve. The longevity data used in the model are taken from published papers on devices implanted in 2008-10 and many are no longer on the market. Increases in projected longevity by manufacturers, and longer warranties tend to suggest manufacturers have confidence that newer devices will last longer but this remains to be proven. More information on the calculation of projected longevity is available in the Technical Report.

4.6 Conclusions on the economic evidence

The company has made the most of the available data in constructing the model. The company's model is based upon observational data which shows that ENDURALIFE-powered CRT-Ds had increased longevity compared to devices from St Jude Medical and Medtronic in 2008-10. Whether the increased longevity delivered a cost saving depends on the purchase cost of the devices. The base case shows that if the devices all have the same purchase cost of £12,404, then ENDURALIFE-powered CRT-Ds in 2008-10 were cost saving. Using list prices supplied by the manufacturers ENDURALIFE-powered CRT-Ds were not cost saving compared with Medtronic CRT-Ds.

The main weakness of the model and published data 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 2016 draft manuscript [42] as ‘recent generation’ are the Consulta (withdrawn 2015), the Maximo II (withdrawn 2016) and the Protecta (withdrawn 2016). [redacted] As device longevity is related to other factors as well as battery technology, past performance is not necessarily indicative of future results.

There have been technology developments other than battery technology that can be expected to impact on device longevity, for example quadripolar devices and improvements to device algorithms. Typically an innovation is developed by one manufacturer and then something similar is adopted by the other players within a short time. These technologies are rapidly evolving in a highly competitive market, and this poses challenges for research and evidence based medicine. By the time evidence is produced the devices may be no longer on the market.

Whilst we have comparative data from clinical studies, these are retrospective, observational studies with a risk of bias.

Some key drivers of the model are based upon assumptions. For example the cost of the technology is assumed to be equal to the cost of comparators. The warranty arrangements are also assumed to be the same for all manufacturers.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The EAC has explored device purchase cost in two ways. Firstly we have used list prices for current technologies supplied by manufacturers. This changes the result of the model from ENDURALIFE-powered CRT-Ds being cost saving, to the point where other manufacturer's devices are less costly, all else being unchanged. Secondly, we used the average selling price for ENDURALIFE-powered CRT-Ds and then allowed the comparator technology prices to fall until the point at which each became cost saving. There is considerable difference between the list prices and the overall average selling price, and it is possible that average selling price per manufacturer is less variable than the list prices. This remains unknown whereas list prices are known.

The EAC has looked at actual warranties based on information supplied by the manufacturers and found that longer warranties offered by the comparator manufacturers reduce the cost saving of the technology but did not change the result from cost saving, all else being unchanged and assuming 100% of warranties are claimed. Where the warranty extends beyond 6 years, this could not be included in the model due to the 6 year time horizon.

The EAC extended the company's sensitivity analysis for complications based on information from clinical experts, but this had a minimal effect on the results.

5 Conclusions

Boston Scientific has submitted the best available evidence and the EAC does not have significant concerns about its quality and robustness. The EAC is concerned about the *applicability* of the evidence to decision-makers today and this weakness was highlighted by the company.

Whether differences in longevity between ENDURALIFE-powered CRT-Ds and comparators lead to a reduction in replacement procedures depends on patient life expectancy.

We have 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 Implications for research

Evidence on ENDURALIFE battery technology incorporated in older technologies is available and shows that ENDURALIFE powered CRT-Ds had better longevity at that time. There is a lack of evidence on the longevity of devices that are powered by ENDURALIFE battery technology and that are currently on the market, and for current competitor devices. While we feel that the ENDURALIFE-powered CRT-Ds have likely continued to be developed, we consider that this is possible also for comparator CRT-Ds, and this does not have to be based on the battery technology in isolation. By the time evidence on current technologies is captured it is likely that the technologies will have developed further. Capturing data on a patient register would allow retrospective evaluation of technologies, but would not assist with decision-making now. Long term clinical outcomes can only be determined in a long term study. Predictive longevity is based on manufacturer bench testing. Bench testing would be more useful if the testing methods used and settings for reporting the predicted longevity were consistent across manufacturers. More detail is available in the technical report.

Appendix 1 Ongoing studies identified by the EAC

The EAC identified three ongoing studies, none of which are directly relevant to the decision problem. These are as follows.

Boston Scientific is sponsoring the CAPTIVATE study, an evaluation of the safety of automatic threshold algorithms used in the AUTOGEN CRT-D. The primary outcome measure is the system-related complication rate at three months. The study is due to complete in June 2017.

Boston Scientific sponsors the ENABLE MRI study (Expanding MRI Access for Patients With New and Existing ICDs and CRT-Ds). The study's objective is to collect data to confirm the safety and effectiveness of the ImageReady™ MR Conditional Defibrillation System when used in the 1.5T MRI environment under the labelled Conditions of Use. The primary outcome measure is the MR scan-related System Complication Free Rate. The study is due to complete in December 2019.

Guidant Corporation sponsors the RallyX4 study (Maximizing CRT Delivery by Using MultipolAr Coronary Sinus Lead FamiLy ACUITY® X4). The objective of this study is to collect clinical data on safety and performance of ACUITY X4® leads when used in a standard clinical setting. The primary outcome measure is the Phrenic Nerve Complication Free Rate. The estimated completion date is December 2016.

Appendix 2 studies of longevity not included

Details of 14 studies comparing CRT-D longevity across manufacturers considered by the EAC but judged to be not relevant to the scope

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Biffi [22]	Abstract	Not reported	Mar 2013-Nov 2014	715 ICDs including 366 CRT-Ds	Median longevity 1728 days for CRT-D devices (4.7 years)	Not known	5-year survival (CRT-D): MDT 26% BSC 74% SJM 50% BTK 28%	Low. Estimated implant period c2008-2009	No
Gakenheimer [23]	Paper	Not reported	Jan 2007-Jan 2011	801 explanted ICDs	Not reported	Not known	Reported graphically only. BSC devices had best longevity.	Low. Estimated implant period c2003-2007	No
Hauser 2010 [24]	Abstract	Not reported	2000-2010	2541 ICDs including 428 CRT-Ds.	Not reported	Not known	No difference between manufacturers found for CRT-Ds	Low. Estimated implant period pre-2008	No

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Hauser 2014 [25]	Abstract	Not reported	2010-2013	1556 Mixed ICD PG & CRT-D. Proportions not reported. % ENDURALIFE-powered CRT-D not known.	Total 100 months (median / mean not reported)	Not known	Not quantified precisely. BSC had greatest longevity, followed by MDT, followed by SJM (p<0.001)	Low. Estimated implant period c2006-2010	No
Horlbeck [26]	Paper	Jun 1988-Jun 2009	-	-	-	None	-	None. No ENDURALIFE-powered devices studied (paper names devices studied).	No

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Johansen [27]	Abstract	2007-2013	Not reported	2793 CRT-Ds: MDT 651 BTK 369 BSC 136 SJM 1587	Not reported	Not known	Battery depletion/device failure rates: MDT 43 (6.7%) BTK 4 (1.1%) BSC 1 (0.7%) SJM 33 (2.1%). 4 year survival: MDT 81.1% BTK 95.8% BSC 95.7% SJM 93.6% Battery depletion was the reason for 88% of device replacements	Limited.	No

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Knops [28]	Paper	Oct 1998-Dec 2006	-	-	-	None	-	None. Implant period precedes 2008. No ENDURALIFE-powered devices studied (paper names devices studied).	No
Manyam [29]	Abstract	2002-2012	Not reported	1338 patients with CRT-D: SJM 304 BSC 279 MDT 755	Median/mean not reported.	Not known	Rate of CRT-Ds reaching ERI within 4 years: SJM 17% BSC 24% MDT 39% Projected longevity overestimated survival in SJM and BSC devices, but MDT projections were accurate.	Low: implant period includes a long pre-2008 interval.	No

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Parisi [30]	Abstract	Not known	Mar 2013-Nov 2014	366 patients with CRT-Ds replaced for battery depletion only: MDT 164 BSC 135 SJM 60 BTK 7	Median/mean not reported	Not known	5 year survival rate: MDT 26% BSC 74% SJM 50% BTK 28% LV output was a predictor of early depletion (HR 1.44, 95% CI 1.28-1.63, p<0.0001). BSC was a protective factor (HR 0.35, 95% CI 0.28-0.44, p<0.0001).	Estimated implant period 2008-2009	No
Salgado [31]	Abstract	Jan 1995 – Dec 2012	Not reported	21 patients with CRT-Ds: BSC/Guidant 15 MDT 1 SJM 5	Median/mean not reported: data imply follow-up to replacement	Not known	Mean (SD) longevity, years: BSC/Guidant 4.52 (0.96) MDT 4.17 (no SD) SJM 4.62 (1.25)	Low. Few CRT-Ds studied. Estimated implant period 1991-2008	No

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Seegers [32]	Paper	1998-2010	Not reported	1665 devices including 593 CRT-Ds	Median/mean not reported. Total = 10 years	3 (COGNIS)	Median generator lifetime (95% CI): MDT 5.7 years (5.5, 5.9) BSC/Guidant 5.4 (5.0,5.4) BTK 5.2 (5.0,5.4)	Low. 3 ENDURALIFE-powered CRT-Ds studied	No
Thijssen [33]	Paper	1996-2011	Not reported	4673 devices including 1853 CRT-Ds: BIO 194 (11%) BSC/Guidant 1005 (54%) MDT 634 (34%) SJM/Ventritex 20 (1%)	Mean 4.1 (SD 3.2) years	Not known	Mean battery longevity (years): BIO 4.7 (SD 0.1) BSC/Guidant 5.3 (SD 0.1) MDT 5.8 (SD 0.2) SJM/Ventritex 5.0 (0.2)	Low: implant period includes a long pre-2008 interval.	No
Zanon 2015 [34]	Abstract	Not reported	Mar 2013 – Nov 2014	715 ICDs including 366 CRT-Ds: MDT 164 BSC 135 SJM 60 BTK 7	Mean/median not reported	Not known	5 year survival: MDT 26% BSC 74% SJM 50% BTK 28%	Limited: estimated implant period c2008-2009	No

Record	Paper / abstract	Implant period	Explant period	Devices studied: ICD, CRT-D, other, mixed	Follow-up	n (ENDURALIFE-powered CRT-Ds)	Reported longevity by manufacturer	Applicability to Scope	Accept as additional evidence?
Zanon 2016 [35] Extension of study above by same team	Abstract	Not reported	Mar 2013 – May 2015	953 patients with ICDs	Mean/median not reported	Not known	BSC showed the longest CRT-D longevity. Median service life (all CRT-D manufacturers) 4.9 (IQR 4.0,5.7) years.	Limited: estimated implant period c2008-2010	No

Appendix 3 Critical Appraisal checklists for longevity studies published as full journal articles

Study identification Alam 2014 , Alam 2016					
Guideline topic:	**Review question no:**				
Checklist completed by: AC					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	~~Yes~~	~~No~~	Unclear	Retrospective study. It is not known why patients received any particular CRT-D device.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	~~Yes~~	No	~~Unclear~~	The paper reports differences in potential confounders across comparison groups
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Baseline characteristics were comparable between patients with devices from different manufacturers, except for differences consisting of higher rates of coronary artery disease (P = 0.037) and higher serum creatinine levels (P = 0.047) for patients in the Boston Scientific group (P = 0.037), and lower rates of hypertension for patients in the Medtronic group (P = 0.031).
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	~~Yes~~	~~No~~	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	~~No~~	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for	Yes	No	Unclear	Of the 746 patients implanted with CRT-ICDs at the hospitals of the University of Pittsburgh Medical Center, 94 were

	differences in length of follow-up)				excluded from the analysis because they were lost to follow-up within a month after device implantation, because they chose to follow-up in a device clinic closer to their place of residence. Device manufacturers of excluded patients were Boston scientific (n = 32), Medtronic (n = 55), and St Jude medical (n = 7) and were in equivalent proportions to the overall cohort. Six patients implanted with CRT-ICDs from Biotronik were excluded from the analysis because of the small number of devices from this manufacturer that precludes meaningful comparison. In 2016 further losses to follow-up (n = 25) appear to be entirely in the Medtronic group.
C2	**a. How many participants did not complete treatment in each group?**				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	~~Yes~~	~~No~~	Unclear	Paper does not show how many patients were censored due to competing risks.
C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	~~Yes~~	No	~~Unclear~~	N/A
D2	The study used a precise definition of outcome	Yes	~~No~~	~~Unclear~~	Data suggest that all devices reaching ERI were replaced due to battery depletion
D3	A valid and reliable method was used to determine the outcome	Yes	~~No~~	~~Unclear~~	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	N/A
D5	Investigators were kept	~~Yes~~	~~No~~	Unclear	N/A

	'blind' to other important confounding and prognostic factors				
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					

Study identification Ellis 2016					
Guideline topic:	**Review question no:**				
Checklist completed by:					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	~~Yes~~	~~No~~	Unclear	Retrospective study. It is not known why patients received any particular CRT-D device.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	~~Yes~~	No	~~Unclear~~	The paper reports differences in potential confounders across comparison groups
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	~~No~~	~~Unclear~~	Minor differences observed by manufacturer in NYHA class, whether 100% pacemaker dependent, and preimplant LVEF. Many more patients were male, which reflects patient population.
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	~~No~~	~~Unclear~~	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	~~No~~	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	~~No~~	~~Unclear~~	N/A
C2	a. How many participants did not complete treatment in each group?				

	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	~~Yes~~	~~No~~	Unclear	Not reported, though paper presents all competing risk events.
C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	~~Yes~~	~~No~~	Unclear	Exclusions not reported. No obviously missing data.

Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?

~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~

Likely direction of effect: not known

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D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D1	The study had an appropriate length of follow-up	Yes	~~No~~	~~Unclear~~	
D2	The study used a precise definition of outcome	Yes	~~No~~	~~Unclear~~	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	~~No~~	~~Unclear~~	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	No	~~Unclear~~	N/A

Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?

~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~

Likely direction of effect:

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Study identification Landolina 2015					
Guideline topic:	**Review question no:**				
Checklist completed by: AC					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	~~Yes~~	~~No~~	Unclear	Retrospective study. It is not known why patients received any particular CRT-D device.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	~~Yes~~	No	~~Unclear~~	The paper reports differences across comparison groups in device parameters only, not patient demographic/morbidity factors Paper makes use of multivariate analysis to overcome confounding
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	No patient factors are reported
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	~~Yes~~	~~No~~	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	~~No~~	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	~~No~~	~~Unclear~~	No substantial differences in follow-up. Reporting of this by group is very clear.
C2	**a. How many participants did not complete treatment in each group?**				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did	~~Yes~~	~~No~~	Unclear	Paper reports how many patients were censored due to competing risks.

	not complete treatment)				
C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	~~No~~	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	~~Yes~~	No	~~Unclear~~	N/A
D2	The study used a precise definition of outcome	Yes	~~No~~	~~Unclear~~	
D3	A valid and reliable method was used to determine the outcome	Yes	~~No~~	~~Unclear~~	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					

Study identification von Gunten 2015					
Guideline topic:	**Review question no:**				
Checklist completed by: AC					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	~~Yes~~	~~No~~	Unclear	Retrospective study. It is not known why patients received any particular CRT-D device. The paper reports on ICDs for out of scope patient indications including VVIs and DDDs in addition to CRT-D.
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	~~Yes~~	No	~~Unclear~~	The paper reports baseline characteristics (demographic, cardiac morbidity, NYHA class, medical therapies) for the entire cohort and not by analysis groups.
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	See above
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	~~Yes~~	~~No~~	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	~~No~~	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	No	~~Unclear~~	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect? Paper does not report this detail.					
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~			
Likely direction of effect: not known.					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	~~Yes~~	~~No~~	Unclear	154 patients in total were lost to follow-up; 189 transferred to other hospitals; and in either case were censored. This is not reported for different analysis groups.
C2	**a. How many participants did not complete treatment in each group?**				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between	~~Yes~~	~~No~~	Unclear	Paper reports how many patients were censored due to competing risks:

	groups in terms of those who did not complete treatment)				822 died 85 underwent heart transplant 189 moved to other hospitals 154 were lost to follow-up These are not reported by analysis groups

C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	~~Yes~~	~~No~~	Unclear	Not reported by analysis groups

Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?		
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~
Likely direction of effect: not known.		

D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	~~No~~	~~Unclear~~	N/A
D2	The study used a precise definition of outcome	Yes	~~No~~	~~Unclear~~	
D3	A valid and reliable method was used to determine the outcome	Yes	~~No~~	~~Unclear~~	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	No	~~Unclear~~	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	~~No~~	Unclear	Unlikely

Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?		
~~Low risk of bias~~	Unclear/unknown risk	~~High risk of bias~~
Likely direction of effect: not known.		

Appendix 4: Cohort study checklist

Specialist Unit for Review Evidence (SURE)
Questions to assist with the critical appraisal of cohort studies[1]

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Citation: Kirkfeldt (2014) *Are there other companion papers from the same study?*	
	~~Yes/ Can't tell/~~ No
1. Is the study design clearly stated?	Yes
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	Yes Population: People receiving CIED treatment Exposure: CIED treatment Comparator: no control. However, comparisons were made based on device type and whether the device was implanted de novo, replaced the generator or carried out an upgrade/lead revision. Outcomes: total number of complications, major complications, minor complications, mortality.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	The setting, location and relevant dates are provided. The study was carried out across all 14 centres that carry out CIED procedures in Denmark from May 2010 to April 2011. The study included a 6 month follow-up in order to capture cumulative complications.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	The only inclusion criterion was that the patient had undergone CIED treatment. All Danish patients who underwent CIED replacement were included; however, patients with epicardial systems were excluded. Therefore, participant selection appears to be fair as all patients who underwent CIED treatment were included.
5. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	A table on patient and procedure characteristics is included. The table is quite comprehensive with age, gender, BMI and centre volume. Procedure characteristics include CIED type,

	procedure type, operator volume and procedure priority.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	The outcomes reported are the complications noted during the study and so are appropriate. The authors have also included mortality as an outcome.
7. Was bias considered? e.g. recall or selection bias	Bias was not considered. However, selection bias would not have been an issue due to the authors including every patient that underwent CIED treatment during May 2010 to April 2011.
8. Is there a description of how the study size was arrived at?	The study included all patients that underwent CIED treatment in Denmark from May 2010 to April 2011. The authors explained that patients who received treatment with epicardial systems were excluded.
9. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	The statistical methods are well described. Between group analyses, in addition to how binary regression was carried out, are described.
10. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	There is no information on participant flow. As this was a retrospective study using patient charts the authors were able to present all information.
11. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	The results are well described with 95% confidence intervals given in addition to p values where required.
12. Is any sponsorship/conflict of interest reported?	The study was supported with research grants from Biotronik and Medtronic. Some of the authors have received speaker fees from Biotronik, Boston-Scientific and Biosense Webster.
13. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors state the following limitations: • Only complications documented on patient charts were identified. • Data on drug regimens undertaken by the patients was not collected and so could confound the results. • The study was not randomised and so confounding factors may not be controlled for. • 6 month complications are deemed to be short-term complications and not

	long-term. The authors state that longer follow-up is important for CIED-related infections.

This checklist should be cited as: Specialist Unit for Review Evidence (SURE) 2016. Questions to assist with the critical appraisal of cohort studies. Available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html

[1] Devised with reference to the STROBE consideration and elaboration article: Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, et al. (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. PLoS Med 4(10): e297. doi:10.1371/journal.pmed.0040297

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