NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

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

Sponsor: Boston Scientific

Date sections A and B submitted: 19 May 2016

Date section C submitted: 17 June 2016

August 2011 (Version 1.1)

Contents

Glossary of terms

Term	Definition
Ah	Ampere Hour
AV	Atrioventricular
BSC	Boston Scientific
BTK	Biotronik
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CIED	Cardiac Implantable Electronic Device
COPD	Chronic Obstructive Pulmonary Disease
CRMD	Cardiac Rhythm Management Device
CRT-D	Cardiac Resynchronisation Therapy with Defibrillation
DC	Dual-Chamber
DDD	Dual-Chamber Defibrillator
DRG	Diagnosis Related Group
EG	Earlier Generation
ERI	Elective Replacement Indicator
FDA	Food and Drug Administration
HR	Hazard Ratio
HRG	Healthcare Resource Group
ICD	Implantable Cardioverter Defibrillator
ICD-DR	Dual Chamber ICD
ICD-VR	Single Chamber ICD
INT	Intermedics
Li/Mn02	Lithium Manganese Dioxide
LBBB	Left bundle branch block

LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MDT	Medtronic
MHRA	Medicines & Healthcare products Regulatory Agency
N/A	Not Applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association classification criteria for heart failure
OMT	Optimal medical therapy
OOS	Out Of Service
OPCS	Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures
OR	Odds Ratio
RCT	Randomised Clinical Trial
RG	Recent generation
RV	Right Ventricular
SC	Single-Chamber
SCD	Sudden Cardiac Death
SJM	St Jude Medical
SLR	Systematic Literature Review
UK	United Kingdom
US	United States
VVI	Single-Chamber Defibrillator
WMD	Weighted Mean Difference

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core

information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]'). Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

The user should enter text at the point marked '[redacted]' or in the tables as appropriate. '[redacted]' text may be deleted.

List of tables and figures

Executive Summary

- CRT-D devices are recommended as a treatment option for people with heart failure, with 2014 NICE guidance (TA 314) expanding the number of patients eligible for the therapy, in a country already lagging behind other European countries in terms of implant rates
- Earlier clinical intervention and aging populations means many patients are outliving their initial devices and are subject to device replacement procedures (which represent ~30% of all implants in England)
- Device longevity (i.e. the number of years the battery is projected to last) is an increasingly important feature of these devices to close the gap between expanding indications and a financially constrained healthcare system
- Boston Scientific's unique ENDURALIFE-powered CRT-D devices incorporate advanced battery technology designed to provide extended device longevity
- The evaluation of the clinical evidence included:
    - 7 observational studies reporting on battery survival;
    - 5 manufacturer-generated Product Performance Reports reporting on device malfunction and survival probability; and
    - 20 studies reporting adverse events associated with replacement procedures
- The evidence demonstrates that:
    - ENDURALIFE-powered CRT-Ds showed the longest battery survival in all 7 studies reported in this analysis [Sections 7.6, 7.8]
    - In addition to manufacturer, battery capacity, battery chemistry, and level of utilisation/drain are main predictors of battery longevity [Sections 7.6, 7.8]
    - Improved longevity can reduce the need for replacement procedures
    - These replacement procedures are associated with complications including lead damage, infections, hematomas, pain, cardiovascular adverse events and death [Sections 7.7, 7.8]
    - Risk of complications is typically higher in patients undergoing device replacement, compared to de novo implants and matched controls without replacement [Sections 7.7, 7.8]
    - Replacement procedures are negatively perceived by patients [Sections 7.7, 7.8]
    - Overall survival probability for CRT-D devices is increasingly more reliant on normal battery depletion than malfunctions over time across all manufacturers and device models [Section 7.6]
- The evaluation of the economic evidence included:
    - 7 articles
    - A de novo economic analysis
- The evidence demonstrated that:
    - The evidence consistently showed a link between an increased device longevity and savings for the healthcare system [Section 8.2, 9.5, 9.8]
    - Results of the de novo cost model show that the 6-year therapy costs of one CRT-D patient would be £22,322 with ENDURALIFE-powered CRT-Ds, with Medtronic and St Jude Medical CRT-Ds 31% and 22% more respectively [Section 9.5.19.5.2]
    - The analysis shows that for the NHS in England, the maximum savings would amount to £44 million over 6 years. This would significantly support the implementation of TA 314 and appropriate patient access to CRT-D therapy – at no increased cost for the NHS [Section 9.5]
- ENDURALIFE-powered CRT-Ds remained a cost-saving option versus the comparators in all sensitivity analyses [Section 9.5.6, 9.5.7, 9.5.8, 9.5.9]

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	**Variation from scope**	**Rationale for variation**
Population	Patients undergoing CRT-D device implantation for heart failure in line with NICE Technology Appraisal 314	None	Not relevant
Intervention	CRT-D devices with ENDURALIFE Battery Technology	Adverse events associated with replacement procedures based on any replacement procedure regardless of comparator	Lack of brand specific evidence
Comparator(s)	CRT-D devices not incorporating ENDURALIFE Battery Technology (see also 'Cost analysis' below)		
Outcomes	The outcome measures to consider include: • Device survival • Battery survival (or time to battery depletion) • CRT-D component failure • Number of invasive procedures including replacement surgeries • Incidence of complications due to replacement procedures for battery depletion and/or CRT-D component failure (as per definitions in the REPLACE registry) • Inpatient admissions; bed days (related to interventions) • Death • Patient satisfaction • Quality of life • Device-related adverse events	None	Not relevant

Cost analysis	Comparator(s): • CRT-D devices not incorporating ENDURALIFE battery technology. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Scenario and sensitivity analyses will be undertaken to address uncertainties in the model parameters including: - Warranty periods - Differences in performance between older and newer devices - Differences in battery performance between older and newer devices	None	Not relevant
Subgroups to be considered	None	None	Not relevant
Special considerations, including issues related to equality	Heart failure can affect people of all ages, but it is more common in older people – more than half of all people with heart failure are over the age of 75. Older people are protected groups under the Equality Act 2010.	None	Not relevant

2

Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Boston Scientific's ENDURALIFE™ Battery Technology has been incorporated into all CRT-D devices commercialised since 2008. This encompasses the following device families:[(a)]

- 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

2.2 What is the principal mechanism of action of the technology?

Cardiac resynchronisation therapy (CRT) is a special form of cardiac pacing aimed at restoring the mechanical (i.e., contraction) synchrony of the two ventricles of the heart – thereby improving ventricular efficiency and blood flow – through electrical stimulation. CRT has been proven in large scale randomised clinical trials to extend life expectancy and improve quality of life and reduce hospital admissions in patients with heart failure.[1] CRT requires high frequency but low power energy consumption.

An implantable cardioverter-defibrillator (ICD) senses and analyses the electrical activity of the heart, thereby monitoring for arrhythmias associated with sudden cardiac death such as ventricular tachycardia or fibrillation. Once detected, the device delivers electrical pulses or shocks (defibrillation therapy) to terminate these dangerous rhythms. A standard ICD can also protect against bradyarrhythmias. For these functions, the ICD requires low frequency but high power energy consumption.

(a) For labelling indications please refer to: http://www.bostonscientific.com/manuals/manuals/landing-page.html

The cardiac resynchronisation therapy with defibrillation (CRT-D) device is an advanced type of ICD capable of delivering CRT as well as treating arrhythmias with defibrillation therapy. It consists of a small battery-powered pulse generator that is implanted under the skin just below the collarbone, with three leads from the generator inserted into the right atrium and both ventricles of the heart. The opposing energy consumption patterns of the two functions place high performance requirements on the pulse generator.

Boston Scientific's unique ENDURALIFE-powered CRT-D devices, first commercially launched in 2008, are the culmination of years of research and development to address these opposing energy demands. The advanced battery technology incorporates high performance battery chemistry, efficient electronics design and up to twice the battery capacity of some other devices without compromising on device size.[2]

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Heart failure is a condition defined as the inability of the heart to efficiently pump blood around the body. It can be caused by structural or functional cardiac disorder that impair the heart's ability to function efficiently; for example, coronary artery disease or high blood pressure which may gradually cause the heart to become stiff or weak. Heart failure patients will often suffer with symptoms such as breathlessness, fatigue and fluid retention. Clinically it is classified according to the New York Heart Association (NYHA) functional classification system shown in table Table A2 below.[3]

Table A2 NYHA Functional Classification System[3]

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Heart failure is also classified according to which part of the heart is not functioning correctly:

- **Left-sided heart failure** is the failure of the left ventricle to effectively pump blood out of the heart; this can be either systolic (when the left ventricle loses the ability to contract properly; also known as left ventricular systolic dysfunction, LVSD) or diastolic (when the left ventricle loses its ability to relax normally and can't properly fill with blood after a contraction; also known as heart failure with preserved ejection fraction)

- **Right-sided heart failure** is the failure of the right ventricle to effectively pump blood to the lungs, resulting in blood and usually occurs as a result of left-sided failure

Cardiac resynchronisation therapy with defibrillator (CRT-D) devices are recommended as treatment options for certain people with heart failure who have left ventricular dysfunction.[1] In line with the scope issued by NICE,[4] the specific heart failure population relevant to this evaluation are those indicated in line with NICE Technology Appraisal 314.[1] Table A3 below summarises the specific patient subgroups indicated for such a device in this guidance.

Table A3 Summary of NICE Guidance TA314: Treatment options with ICD or CRT for people with heart failure who have left ventricular dysfunction with an LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB)[1]

QRS	LBBB	NYHA I	NYHA II	NYHA III	NYHA IV
< 120 ms	N/A	ICD*	ICD*	ICD*	OMT
120 -149 ms	Without LBBB	ICD	ICD	ICD	CRT-P
	With LBBB	ICD	CRT-D	CRT-P or -D	CRT-P
≥ 150ms	With or without LBBB	CRT-D	CRT-D	CRT-P or -D	CRT-P

* If there is a risk of sudden cardiac death

Heart failure is a chronic condition predominantly affecting people over the age of 50 years. The incidence of heart failure in the UK is 140 per 100,000 men and 120 per 100,000 women. Approximately 900,000 people in England and Wales have heart failure, of which at least half have left ventricular systolic dysfunction, with the incidence and prevalence of heart failure increasing with age.[1]

Costing work[5] to support NICE's guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure[1] estimated that based on the treatment recommendations as shown in Table A3 above, there would be approximately 7,199 cardiac resynchronisation therapy-with defibrillator (CRT-D) implant procedures annually in England, including replacement procedures.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

The following are considered relevant national guidelines and guidance related to ENDURALIFE-powered CRT-D devices:

(1) NICE TA314 (June 2014):[1] Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA 95 and TA 120)

(2) NICE CG108 (August 2010):[6] Chronic heart failure in adults: management

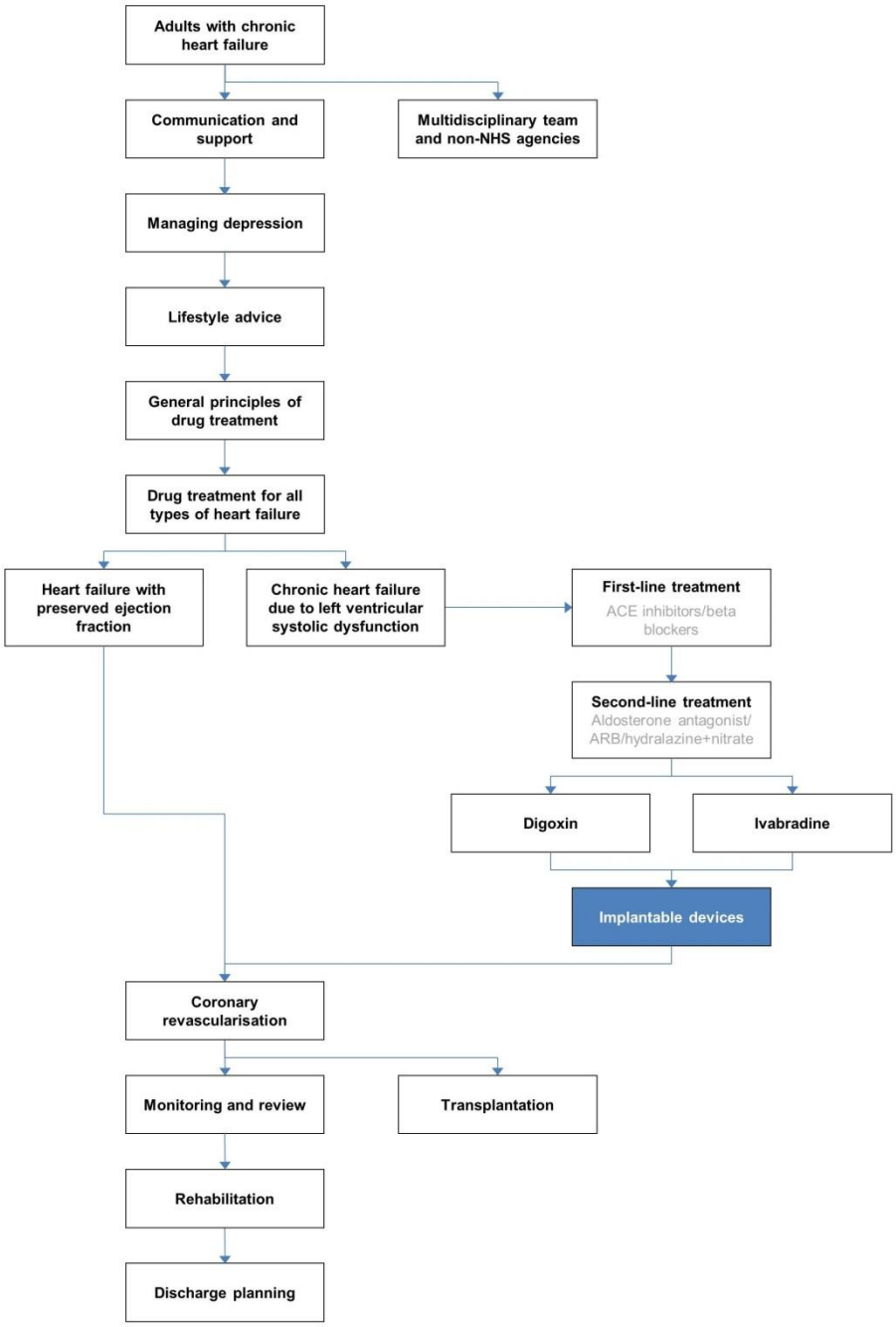
The NICE technology appraisal TA314 guidance recommends cardiac resynchronisation therapy with defibrillation (CRT-D) devices as a possible treatment for certain people with heart failure due to left ventricular dysfunction.[1] Table A3 above summarises the specific patient subgroups indicated for such a device in this guidance.

The NICE clinical guidelines CG108[6] refers to NICE's technology appraisal TA120 for recommendations on cardiac resynchronisation therapy for the management of chronic heart failure patients.[7] This guidance has subsequently been updated and is replaced by technology appraisal guidance TA314.[1]

3.3 * Describe the clinical pathway of care that includes the proposed use of the technology.

CRT-D devices are recommended as an adjunctive treatment option for chronic heart failure patients on optimal medial therapy who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less.[1] The NICE Pathway for managing chronic heart failure[8] is shown below in Figure A1.

Figure A1 NICE Pathway: Managing chronic heart failure (as of 11 May 2016)[8]



3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

With earlier clinical intervention and aging populations, many patients are now living longer than their initial devices and are subject to device replacement procedures. In England, replacements of implantable defibrillator devices (including ICDs as well as CRT-Ds) already represent around a third of the total number of implant procedures

and have increased 30% between 2010/11 and 2014/15.[9] These replacement procedures have a higher likelihood of complications and infections versus patients not undergoing these procedures, which can negatively impact mortality.[38,41,43]

Alongside this already high number of replacement is an overall growth in the number of patients receiving these devices, which is adding further pressure to the healthcare system. Currently the UK is underpenetrated compared to other developed European countries in terms of implanting CRT-D devices,[10] which implies that some eligible patients may not be treated at present. To close this gap, and to implement the updated NICE guidance on ICD and CRT-D devices published in June 2014 (which expanded the indications and recommended these devices for more patients),[1,5] further expansion of the population who should be receiving these devices is needed which will exacerbate the situation.

Increased battery longevity and the associated reduction in avoidable replacement procedures could be one approach to addressing these concerns. However, currently this factor is often given poor or no consideration when making procurement decisions – particularly in terms of the economic as well as clinical implications.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

Implantation of an ENDURALIFE-powered CRT-D device uses standard techniques and follow up is as for any other CRT-D device. As such, the pathway of care for chronic heart failure patients would remain unchanged by the use of ENDURALIFE-powered CRT-D devices.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

The use of ENDURALIFE-powered CRT-D devices in existing centres implanting CRT-D devices is not expected to have an impact on the way current services are organised or delivered. However, the recent introduction of centralised procurement for High Cost Devices in England (of which CRT-D devices are one) will likely have a considerable impact on device availability going forwards.[11]

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests, investigations or administrative requirements are needed when selecting or monitoring those patients who receive an ENDURALIFE-powered CRT-D device.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure will need to be used alongside ENDURALIFE-powered CRT-D devices for the claimed benefits to be realised.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

ENDURALIFE Battery Technology allows for extended longevity in Boston Scientific's ENDURALIFE-powered CRT-D devices, i.e., a device which will last longer before the battery needs to be replaced. Throughout a patient's lifetime, this extended battery life could increase the time between replacements and therefore reduce the number of avoidable replacement procedures.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

Both de novo and replacement procedures to implant CRT-D devices are commissioned as a specialised service by NHS England under the Complex Invasive Cardiology Clinical Reference Group.[12] Through the increased use of CRT-D devices

with longer battery life, the number of avoidable replacement procedures due to early battery depletion of the device could be reduced. Furthermore, this reduction in number of replacement surgeries can also reduce the risk of complications and infections associated with these procedures. Disinvesting in these activities would allow NHS England resources to be used in the most efficient way – and in particular, to ensure the NICE Technology Appraisal 314[1] is fully implemented so as to improve treatment rates for indicated heart failure patients (as highlighted in sections 3.1 and 3.4 above).

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- **instructions for use**
- **CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity**
- **quality systems (ISO 13485) certificate (if required).**

Documents attached.

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

All ENDURALIFE-powered CRT-D devices listed in section 2.1 above have a relevant CE mark for the indication specified in the scope issued by NICE. Table A4 below provides the date authorisation was received for the relevant device families.

Table A4 CE mark authorisation for ENDURALIFE-powered CRT-D devices

Device Families	**Date of first issue of CE mark**
COGNIS™ CRT-D Family	17 January 2008
ENERGEN™ CRT-D Family PUNCTUA™ and PUNCTUA™ NE CRT-D Family INCEPTA™ CRT-D Family	6 October 2010
AUTOGEN™ CRT-D Family INOGEN™ CRT-D Family DYNAGEN™ CRT-D Family ORIGEN™ CRT-D Family	15 October 2013

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The AUTOGEN™, INOGEN™, DYNAGEN™, ORIGEN™, INCEPTA™, ENERGEN™, PUNCTUA™ and COGNIS™ CRT-D devices have been marketed in

the US, the European Economic Community, Australia, New Zealand, Canada and countries within Latin America, Asia, Africa, and the Middle East.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

ENDURALIFE-powered CRT-D devices were first launched in the UK in February 2008 and have been commercially available since then under the brand names listed in section 2.1.

4.5 If the technology has been launched in the UK provide information on the use in England.

ENDURALIFE-powered CRT-D device have been used by all major NHS hospitals implanting CRT-D devices.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

The following study[13] summarised in Table A5 is currently being conducted by Boston Scientific and is relevant to the decision problem. However, there are no plans for additional evidence to be made available in the next 12 months.

Table A5 Summary of ongoing study relevant to the decision problem

Study name	LONGEVITY Study. Evaluation of the Device and Battery Longevity of Boston Scientific Market-released ICD and CRT-D Devices
Study Identifier	NCT02091011
Design	Prospective, non-comparative single arm observational cohort study to assess rate and cause of device replacements for Boston Scientific ICDs and CRT-Ds at 5 years post-implantation
Enrolment[14]	N=1,600 (enrolment completed 26 February 2016), of which: • US – 1347 • Canada – 106 • Korea – 47 • United Kingdom – 19 • Japan – 51 • Spain – 24 • Germany – 5 • Switzerland – 1
Estimated Study Completion Date	May 2021

We are also aware of an ongoing analysis being conducted based on the UK British Heart Rhythm Society/NICOR Cardiac Rhythm Management National Clinical Audit registry focusing on device longevity. We are unclear as to the progress of this analysis nor the publication plans and therefore cannot confirm when this may become available.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

We are not aware of any additional planned assessments of ENDURALIFE-powered CRT-D devices in the UK at present.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

There are no equality issues related to the use of ENDURALIFE-powered CRT-D devices for any appropriately selected patient.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

There are no known equality issues relating to the assessment of the technology that may require special attention.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

Not relevant.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

Summary of clinical evidence

- The evaluation of the clinical evidence included:
  - 7 observational studies reporting on battery survival;
  - 5 manufacturer-generated Product Performance Reports reporting on device malfunction and survival probability; and
  - 20 studies reporting adverse events associated with replacement procedures
- The evidence demonstrates that:
  - ENDURALIFE-powered CRT-Ds showed the longest battery survival in all 7 studies reported in this analysis [Sections 7.6, 7.8]
  - In addition to manufacturer, battery capacity, battery chemistry, and level of utilisation/drain are main predictors of battery longevity [Sections 7.6, 7.8]
  - Improved longevity can reduce the need for replacement procedures
  - These replacement procedures are associated with complications including lead damage, infections, hematomas, pain, cardiovascular adverse events and death [Sections 7.7, 7.8]
  - Risk of complications is typically higher in patients undergoing device replacement, compared to de novo implants and matched controls without replacement [Sections 7.7, 7.8]
  - Replacement procedures are negatively perceived by patients [Sections 7.7, 7.8]
  - Overall survival probability for CRT-D devices is increasingly more reliant on normal battery depletion than malfunctions over time across all manufacturers and device models [Section 7.6]

7.1 Identification of studies

A systematic literature review was conducted to identify relevant studies focused on comparative effectiveness of ENDURALIFE-powered CRT-Ds vs other similar CRT-Ds, in terms of:

(i) overall device survival

(ii) battery survival

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

A systematic approach to identifying clinical and background literature was followed, analysing the sources:

(i) Pubmed

(ii) Cochrane

(iii) ClinicalTrial.gov

Additionally, hand-searching of internal company documentation was order to find studies not indexed. Please refer to the PRISMA diagram in Figure C1 PRISMA flow diagram for economic search for the algorithm of search.

This review is based on a search conducted on April 28th 2016. The studies identified were independently assessed by a reviewer in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by this second reviewer. See Appendix 1 for full details of the search strategy used.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Hand-searching of internal company documentation was performed to identify any relevant unpublished data. In addition, publicly available Product Performance Reports from all manufacturers were reviewed to assess their relevance to the scope – specifically in relation to the outcomes of device survival and device component failure included in the statement of the decision problem,[4] which we do not believe are well addressed in the published literature.

7.2 Study selection

Published studies

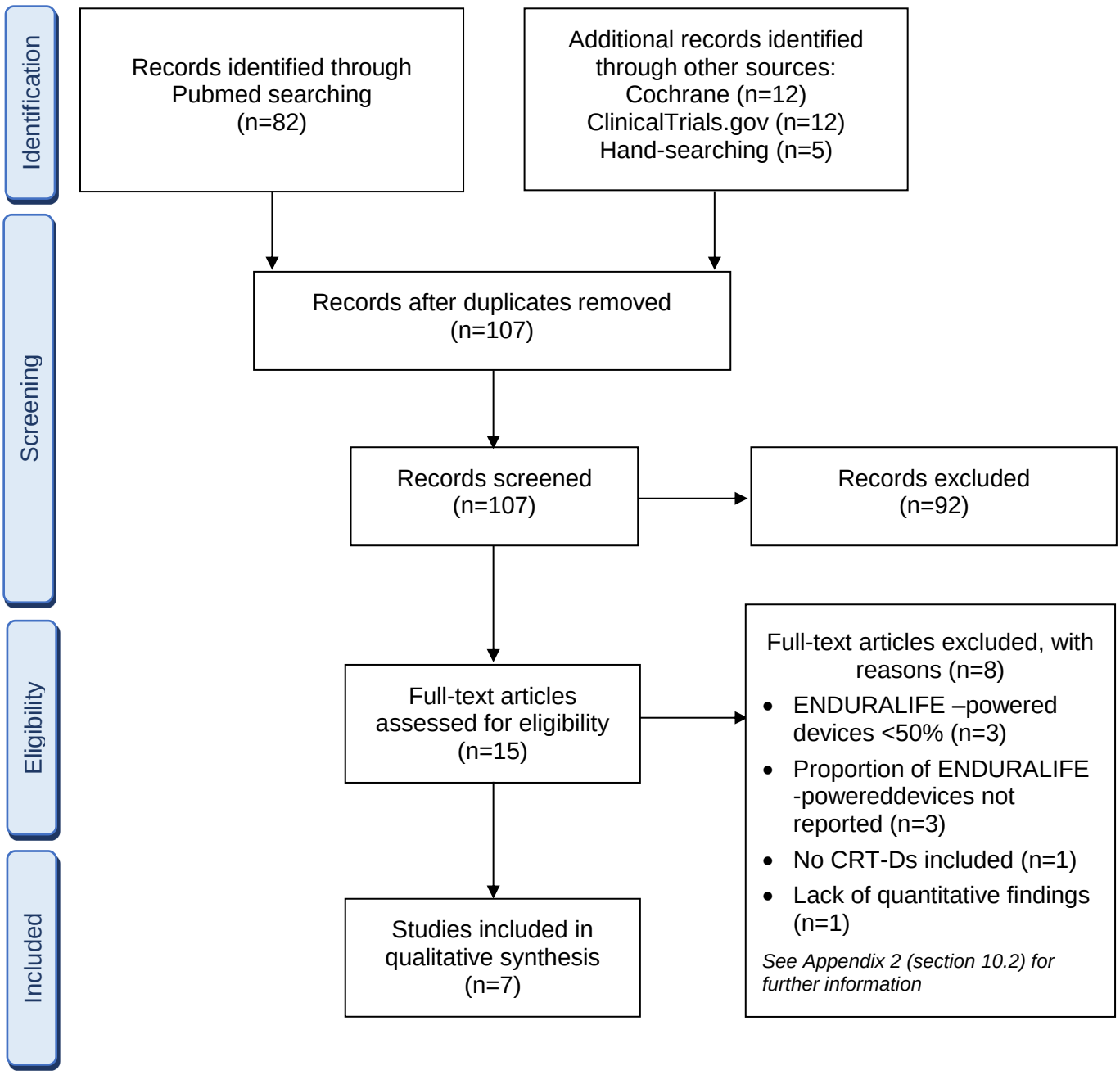
7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Patients implanted with CRT-Ds
Interventions	• ENDURALIFE-powered CRT-Ds (Boston Scientific)
Outcomes	Device and battery survival/longevity; time to reaching ERI; predictors of battery survival
Study design	All studies (conducted in experimental or observational setting) comparing CRT-D outcomes by technology/manufacturer and evaluating the ENDURALIFE Battery Technology
Language restrictions	English language only
Other restrictions	Full text or abstract available
Search dates	Articles published between 2008 and 2016
Exclusion criteria	
Population	Patients implanted exclusively with ICDs (i.e. ICD-VR, ICD-DR, not CRT-Ds)
Interventions	Studies where: - ENDURALIFE-powered CRT-Ds represented less than 50% of the overall BSC implanted CRT-D devices, AND/OR the proportion of ENDURALIFE-powered CRT-Ds was not clearly reported AND/OR - A subgroup analysis on ENDURALIFE-powered CRT-Ds was not conducted
Outcomes	-
Study design	Non-comparative studies/editorials/reviews
Language restrictions	English language only
Other restrictions	No full text or abstract available
Search dates	Articles published prior to 2008 (antecedent to the date of market authorisation of the first ENDURALIFE-powered CRT-D device)

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure B1 PRISMA flow diagram for longevity search



Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Patients implanted with CRT-Ds
Interventions	ENDURALIFE-powered CRT-Ds (Boston Scientific)
Outcomes	Device and battery survival/longevity; time to reaching ERI; predictors of battery survival
Study design	All studies or company-reported product performance data reporting CRT-D outcomes by technology/manufacturer
Language restrictions	-
Search dates	Articles published between 2008 and 2016; most recent publication of company-reported performance data
Exclusion criteria	
Population	Patients implanted exclusively with ICDs (i.e. ICD-VR, ICD-DR, not CRT-Ds)
Interventions	Analyses not showing findings of CRT-D (i.e. lack of subgroup analyses on CRT-D population only)
Outcomes	-
Study design	-
Language restrictions	-
Search dates	-
Search dates	-

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

No unpublished studies were excluded.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

The present review considers 7 observational, predominantly retrospective, published studies which reported on battery survival of ENDURALIFE-powered CRT-D devices, various competitor CRT-D devices and Boston Scientific earlier generation CRT-D devices. See the table below for more details on the published studies selected.

Table B3 List of relevant published studies

Study name	Primary study reference	Population	Intervention	Comparator
Alam 2016[15]	Battery longevity from cardiac resynchronization therapy defibrillators: differences between manufacturers and discrepancies with published product performance reports	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude
Ellis 2016[16]	Ampere Hour (Ah) as a Predictor of Cardiac Resynchronization Defibrillator Pulse Generator Battery Longevity: A Multicentre Study	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude
Landolina 2015[17]	Longevity of implantable cardioverter defibrillators for cardiac resynchronization therapy in current clinical practice: an analysis according to influencing factors, device generation, and manufacturer	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude • Biotronik • Sorin
Lau 2015[18]	Large Capacity LiMnO2 Batteries Extended CRTD Longevity in Clinical Use Compared to Smaller Capacity LiSVO Batteries Over 6 Years	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude
von Gunten 2015[19]	Longevity of implantable cardioverter defibrillators: a comparison among manufacturers and over time	Patients implanted with ICDs and CRT-Ds (26.3% of devices included in the analysis)	Boston Scientific	• Medtronic • St. Jude • Biotronik • Sorin • Intermedics
Alam 2014[20]	Battery longevity in cardiac resynchronization therapy implantable cardioverter defibrillators	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude
Williams 2014[21]	Contemporary Cardiac Resynchronization Implantable Cardioverter Defibrillator Battery Longevity in a Community Hospital Heart Failure Cohort	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude

Table B4 List of relevant unpublished studies

Study name	Primary study reference	Population	Intervention	Comparator
Biotronik PPR January 2016[22]	Cardiac Rhythm Management Product Performance Report January 2016	Patients implanted with CRT-Ds	Biotronik	Not applicable – individual company performance data
Boston Scientific PPR Q1 2016[23]	Rhythm Management Product Performance Report Q1 2016, Boston Scientific		Boston Scientific	
Medtronic PPR 2015 Second Edition[24]	Cardiac Rhythm Heart Failure Product Performance Report 2015 Second Edition - Issue 73		Medtronic	
Sorin PPR November 2015[25]	Cardiac Rhythm Management Product Performance Report November 2015, LivaNova		Sorin	
St Jude Medical PPR 2016 First Edition[26]	Implantable Electronic Systems Product Performance Report 2016 1st Edition, St Jude Medical		St Jude	

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

None of the studies listed in Table B3 or Table B4 were excluded.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

No RCTs relevant to the submission were identified. Methodologies for remaining studies are summarised in tables B7.1-B7.7 below.

Published Studies

Table B5 Summary of methodology for randomised controlled trials

Removed; not relevant

Table B7. 1 Summary of methodology for observational studies - Alam 2016

Study name	Alam 2016[15]
Objective	To compare battery longevity by manufacturer
Location	US
Design	• Retrospective • Single centre • Patients enrolled from January 2008 to December 2010
Duration of study	• Mean follow-up: 3.4 (SD=±2.1) years • Maximum possible observation period: 95 months
Patient population	Patients implanted with CRT-Ds
Sample size	• N=621 patients • N=661 devices
Inclusion criteria	Patients implanted with CRT-Ds
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Comparison by manufacturer: • Boston Scientific=173 *(122 of which ENDURALIFE-powered CRT-D, 71%)*[(a)] • Medtronic=391 • St. Jude=57
Baseline differences	Evaluated in a previous study (Alam 2014); statistically significant differences found in: • Coronary artery disease distributions • Serum creatinine distributions
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Evaluated in a previous study (Alam 2014); • Scheduled visits (frequency not specified) • Monitored data: pacing burden, programmed voltage pulse width outputs, pacing lead impedance
Statistical tests	• Log-rank for survival curves comparisons • Chi-square for categorical variable comparison by manufacturer • Threshold for statistical significance: P=0.0500
Primary outcomes (including scoring methods and timings of assessments)	• Rate of device replacement for battery reaching ERI • Time to battery depletion (HR)
Secondary outcomes (including scoring methods and timings of assessments)	Time to battery depletion adjusted for unbalanced electrical pacing parameters between devices from different manufacturers

(a) Proportion of ENDURALIFE-powered CRT-D derived from Alam 2014. See Appendix 3 for details on models included.

Table B7. 2 Summary of methodology for observational studies - Ellis 2016

Study name	Ellis 2016[16]
Objective	To compare battery longevity by Ah (Ampere hour)
Location	US
Design	• Retrospective • Multi-centre (number of centres not specified) • Patients enrolled from August 2008 to December 2010
Duration of study	• Mean follow-up: 3.0 (SD=±1.3) years • Maximum possible observation period: 77 months
Patient population	Patients implanted with CRT-Ds
Sample size	• N=1,302 patients • N=1,302 devices
Inclusion criteria	Patients implanted with CRT-Ds
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Comparison by Ah: • 2.0 Ah (Boston Scientific)=322 *(312 of which ENDURALIFE-powered CRT-D, 97%)*[(a)] • 1.0 Ah (Medtronic)=794 • 1.4 Ah (St. Jude)=186
Baseline differences	Statistical significant differences found in: • Sex • NYHA (New York Heart Association classification criteria for heart failure) classification • Level of pacemaker dependence • Left ventricular Ejection fraction (LVEF) before device implantation
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Scheduled visits (frequency not reported)
Statistical tests	• F-test • Threshold for statistical significance: P=0.0500
Primary outcomes (including scoring methods and timings of assessments)	Proportion of batteries reaching ERI
Secondary outcomes (including scoring methods and timings of assessments)	Predictors of ERI OOS

(a) See Appendix 3 for details on models included.

Table B7.3 Summary of methodology for observational studies - Landolina 2015

Study name	Landolina 2015[17]
Objective	To compare battery longevity by manufacturer and generation (earlier-generation, EG, and recent-generation, RG) defined as the most recent device families released on the market (pre/post 2007)
Location	Italy
Design	• Prospective • Multi-centre (9 centres) • Patients enrolled from January 2008 to March 2010
Duration of study	• Median follow-up: 3.6 years • Maximum possible observation period: 63 months
Patient population	Patients implanted with CRT-Ds
Sample size	• N=1,726 patients • N=1,726 devices
Inclusion criteria	Patients implanted with CRT-Ds
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Comparison by manufacturer and generation: • Boston Scientific=291 RG; 317 EG *(100% of which ENDURALIFE-powered CRT-D among recent generation devices)* [(a)] • Biotronik=20 RG; 29 EG • Medtronic=532 RG; 266 EG • Sorin=69 RG; 30 EG • St. Jude=106 RG; 66 EG
Baseline differences	Not reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	• Log-rank for survival curves comparisons • Fisher/Chi-square for categorical variable comparison by manufacturer • Threshold for statistical significance: P=0.0500
Primary outcomes (including scoring methods and timings of assessments)	Survival from device replacement for battery depletion
Secondary outcomes (including scoring methods and timings of assessments)	Predictors of device replacement for battery depletion

(a) See Appendix 3 for details on models included.

Table B7.4 Summary of methodology for observational studies - Lau 2015

Study name	Lau 2015[18]
Objective	To compare battery longevity by battery characteristics (capacity and chemistry)
Location	UK
Design	• Retrospective • Single centre • Patients enrolled in the period 2008-2009
Duration of study	Maximum follow-up available: 6 years
Patient population	Patients implanted with CRT-Ds
Sample size	• N=155 patients • N=155 devices
Inclusion criteria	Patients implanted with CRT-Ds
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Comparison by manufacturer: • Boston scientific=27 *(27 of which ENDURALIFE-powered CRT-D, 100%)*[(a)] • St. Jude=66 • Medtronic=62
Baseline differences	Not reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	• Log-rank for survival curves comparisons • Threshold for statistical significance: P=0.0500
Primary outcomes (including scoring methods and timings of assessments)	Device survival until ERI
Secondary outcomes (including scoring methods and timings of assessments)	None reported

(a) See Appendix 3 for details on models included.

Table B7.5 Summary of methodology for observational studies - von Gunten 2015

<table>
<tr><td>Study name</td><td>von Gunten 2015[19]</td></tr>
<tr><td>Objective</td><td>To compare battery longevity by manufacturer (before/after 2006)</td></tr>
<tr><td>Location</td><td>Netherlands; Switzerland</td></tr>
<tr><td>Design</td><td>• Retrospective
• Multi-centre (2 centres)
• Patients enrolled from March 1994 to January 2014</td></tr>
<tr><td>Duration of study</td><td>• Median follow-up: 4.4 years
• Maximum possible observation period: 123 months</td></tr>
<tr><td>Patient population</td><td>Patients implanted with VVI-ICDs, DDD-ICDs, CRT-Ds</td></tr>
<tr><td>Sample size</td><td>• N=3,436 patients
• N=4,881 devices
• N=1,284 CRT-Ds</td></tr>
<tr><td>Inclusion criteria</td><td>Patients implanted with VVI-ICDs, DDD-ICDs, CRT-Ds</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Intervention(s) (n =) and comparator(s) (n =)</td><td>Comparison by manufacturer and device type:
<table>
<tr><th></th><th>VVI</th><th>DDD</th><th>CRT-D(a)</th></tr>
<tr><td>Biotronik</td><td>645</td><td>346</td><td>228</td></tr>
<tr><td>Boston Scientific</td><td>413</td><td>275</td><td>259†</td></tr>
<tr><td>Intermedics</td><td>21</td><td>0</td><td>0</td></tr>
<tr><td>Medtronic</td><td>449</td><td>182</td><td>267</td></tr>
<tr><td>St Jude</td><td>625</td><td>388</td><td>526</td></tr>
</table>
†100 of which ENDURALIFE-powered CRT-D(b), 39%; subgroup analysis on ENDURALIFE-powered CRT-Ds shown in the article supplementary material</td></tr>
<tr><td>Baseline differences</td><td>Not reported; only statistics regarding the overall population were shown</td></tr>
<tr><td>How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up</td><td>Scheduled visits (frequency not reported)</td></tr>
<tr><td>Statistical tests</td><td>• Log-rank for survival curves comparisons
• Threshold for statistical significance: P=0.0500</td></tr>
<tr><td>Primary outcomes (including scoring methods and timings of assessments)</td><td>Proportion of battery survival (longevity) at 4, 5, 6 years</td></tr>
<tr><td>Secondary outcomes (including scoring methods and timings of assessments)</td><td>None reported</td></tr>
</table>

(a) In the result section we will focus on CRT-D comparisons leaving out findings related with ICD.

(b) See Appendix 3 for details on models included.

Table B7.6 Summary of methodology for observational studies - Alam 2014

Study name	Alam 2014[20]
Objective	To compare battery longevity by manufacturer
Location	US
Design	• Retrospective • Single centre • Patients enrolled from January 2008 to December 2010
Duration of study	• Mean follow-up: 2.7 (SD=±1.5) years • Maximum possible observation period: 63 months
Patient population	Patients implanted with CRT-Ds
Sample size	• N=646 patients • N=661 devices
Inclusion criteria	Patients implanted with CRT-Ds
Exclusion criteria	• N=94 were excluded from the analysis because they were lost to follow-up • N=6 patients implanted with CRT-Ds from Biotronik were excluded
Intervention(s) (n =) and comparator(s) (n =)	Comparison by manufacturer: • Boston Scientific=173 *(122 of which ENDURALIFE-powered CRT-D, 71%)*[(a)] • Medtronic=416 • St. Jude=57
Baseline differences	Statistically significant differences found in: • Coronary artery disease distributions • Serum creatinine distributions
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	• Scheduled visits (frequency not specified) • Monitored data: pacing burden, programmed voltage pulse width outputs, pacing lead impedance
Statistical tests	• Log-rank for survival curves comparisons • Chi-square for categorical variable comparison by manufacturer • Threshold for statistical significance: P=0.0500
Primary outcomes (including scoring methods and timings of assessments)	• Rate of device replacement for battery reaching ERI • Battery survival at 4 years
Secondary outcomes (including scoring methods and timings of assessments)	Predictors of battery depletion

(a) See Appendix 3 for details on models included.

Table B7.7 Summary of methodology for observational studies - Williams 2014

Study name	Williams 2014[21]
Objective	To compare battery longevity by manufacturer
Location	US
Design	• Retrospective • Single centre • Patients enrolled from July 2008 to July 2010
Duration of study	• Average follow-up: 4 (SD=±0.8) years • Maximum possible observation period: 64 months
Patient population	Patients implanted with CRT-Ds
Sample size	• N=90 patients • N=91 devices
Inclusion criteria	Patients implanted with CRT-Ds
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Comparison by manufacturer: • Boston Scientific=53 *(51 of which ENDURALIFE-powered CRT-D, 96%)*[(a)(b)] • Medtronic=28 • St. Jude=10
Baseline differences	Not reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Not reported
Statistical tests	• Log-rank for survival curves comparisons • Threshold for statistical significance: P=0.0500
Primary outcomes (including scoring methods and timings of assessments)	Rate of device replacement for battery reaching ERI
Secondary outcomes (including scoring methods and timings of assessments)	Multivariate Cox proportional hazard model to evaluate the covariates that can affect time to battery depletion

(a) See Appendix 3 for details on models included.

(b) Personal communication from Dr Williams, May 2016

Unpublished studies

Product Performance Reports contain performance data for both pulse generators and leads, including CRT-D devices as well as ICDs, CRT-Ps and pacemakers. In line with the published scope for this review, for the remainder of the submission we focus explicitly on PPR data published for CRT-D pulse generators only.

Table B6 Summary of methodology for unpublished studies

Study name	Biotronik PPR January 2016[22]	Boston Scientific PPR Q1 2016[23]	Medtronic PPR 2015 Second Edition[24]	Sorin PPR November 2015[25]	St Jude Medical PPR 2016 First Edition[26]
Objective	To present performance data for CRT-D pulse generators prepared in accordance with ISO 5841-2:2014(E), the AdvaMed Industry Guidance for Uniform Reporting of Clinical Performance				
Design	Observational review based on devices returned for analysis				
Duration of study	• Devices implanted to 30 June 2015 • Maximum possible observation period: 72 months	• Devices implanted to 13 January 2016 • Maximum possible observation period: 84 months	• Devices implanted to 2 November 2015 • Maximum possible observation period: 80 months	• Devices implanted to 30 June 2015 • Maximum possible observation period: 121 months	• Devices implanted to 31 December 2015 • Maximum possible observation period: 120 months
Patient population	• US registered CRT-D implants	• US registered CRT-D implants • WW distributed CRT-D implants	• US registered CRT-D implants	• Unclear	• US registered CRT-D implants • WW distributed CRT-D implants
US registered CRT-D implants	N=20,790 devices	N=141,000 devices	N=390,624 devices	n/a	N=187,663 devices
Inclusion criteria	• Devices registered and implanted & in-service • Devices returned for analysis[(a)]				
Exclusion criteria	• Devices removed for clinical reasons unrelated to the device's performance (i.e., infection), concurrent events such as morbidity and voluntary explants for other reasons (e.g., device upgrade) • Products no longer being distributed with < 500 active implants • Models or device families with ≤ 10,000 cumulative implant months • Intervals with a population sample of < 200 devices				

Study name	Biotronik PPR January 2016[22]	Boston Scientific PPR Q1 2016[23]	Medtronic PPR 2015 Second Edition[24]	Sorin PPR November 2015[25]	St Jude Medical PPR 2016 First Edition[26]
Intervention(s) (n =) and comparator(s) (n =)	Comparison by product family (versions HF/HFT): • Ilesto 7 = 3,410 • Lumax 340 = 5,310 • Lumax 540 = 8,660 • Lumax 740 = 3,410	Comparison by product family: • Autogen = n/a • Dynagen/Inogen/ Origen = 15,000 • Incepta/Energen/ Punctua = 51,000 • Cognis = 75,000	Comparison across device models from various product families: • InSync Sentry & Maximo = 50,130 • Concerto & Concerto II = 96,556 • Consulta = 67,856 • Maximo II = 30,166 • D3xxTRx[(b)] = 64,096 • Blackwell[(c)] = 81,820	Comparison by product family: • Alto • Ovatio • Intensia • Paradym • Paradym 2 • Paradym RF	Comparison across device models from various product families: • Quadra Assura =52,251 • Unify Assura = 26,186 • Unify Quadra = 11,451 • Unify = 39,452 • Promote + = 15,545 • Promote RF = 24,001 • Atlas + HF = 18,777
Baseline differences	Not reported	Not reported	Not reported	Not reported	Not reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Passive observation based on: • device registration and tracking systems (including decedent searches via US Social Security Administration) • analyses of returned products from all sources				
Statistical tests	n/a	n/a	n/a	n/a	n/a

Study name	Biotronik PPR January 2016[22]	Boston Scientific PPR Q1 2016[23]	Medtronic PPR 2015 Second Edition[24]	Sorin PPR November 2015[25]	St Jude Medical PPR 2016 First Edition[26]
Primary outcomes (including scoring methods and timings of assessments)	• All-cause device survival curves (comprising devices exhibiting normal battery depletion + malfunctions) • Confirmed malfunction free survival curves(d) • Number of devices classified as exhibiting normal battery depletion and malfunction, including malfunction with compromised therapy and malfunction without compromised therapy (tabular form)				

(a) Inclusion criteria relevant for confirmed malfunctions only; unconfirmed malfunctions & inactive but unreturned devices are considered in all-cause device survival curves but excluded from malfunction reporting

(b) Includes Protecta, Protecta XT, Cardia and Egida CRT-D devices

(c) Includes Viva S, Viva Quad S, Viva XT, Viva Quad XT, Viva Quad C, Brava and Brava Quad CRT-D devices

(d) Excludes normal battery depletions

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Alam 2016[15] is an extension to the Alam 2014[20] study. Data used in Alam 2016[15] was derived from Alam 2014[20] (included in this review). The differences between the studies are listed in the table below:

Parameter	Alam 2014[20]	Alam 2016[15]	Notes
Sample size	N=646	N=621	The analysis conducted in the Alam 2016 publication considered the same population enrolled in the Alam 2014 publication, with the exception of N=25 patients implanted with MDT devices, who were excluded (comparison of patients' population at baseline). The reasons of this exclusion are not in mentioned in the publication.
Median follow-up	2.7 years	3.4 years	In the Alam 2016 publication, the last access to patients' medical records was on 20 December 2015, vs 15 April 2013 in the Alam study 2014.

- Although the Alam 2016[15] and Alam 2014[20] studies analysed the same cohort (with the exception of N=25 observations), they provided different outcomes, which were worth reporting.
- The only outcome that the two studies have in common was the rate of battery depletion. However, the outcome was observed at two different time points:
    - Alam 2016[15]: median follow-up=3.4 years
    - Alam 2014[20]: median follow-up=2.7 years

  A note regarding the median follow up of the 2 studies is also reported at the bottom of Table B9.1

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

The search criteria and exclusion parameters for studies were applied to ensure, as far as possible, that the included studies have similar patient populations and methodology:

- All studies were designed to evaluate the probability of device replacement due to battery depletion
- Most studies exclusively enrolled patients implanted with CRT-Ds devices. For the remaining articles, a sub-analysis of the CRT-D subgroup was available
- Implantation of cardiac defibrillators was recommended (by treatment guidelines) if patients met objective indications; this ensures that patients have comparable clinical characteristics and that the evaluated outcome is consistent across the different studies

For unpublished data from Product Performance Reports,[22-26] the methodology for analysing and reporting data is in accordance with ISO 5841-2:2014(E) for all manufacturers. Key definitions as defined by this standard include the following:[27]

Confirmed Malfunction	**Pulse generator performance while implanted and in service resulting from characteristics outside the performance limits established by the manufacturer and confirmed by laboratory analysis. Does not include changes to pulse generator characteristics due to normal battery depletion. Does not include induced malfunctions.**
Malfunctions with Compromised Therapy	The condition when a device is found to have “malfunctioned”, as defined above, in a manner that compromised pacing or defibrillation therapy (including complete loss or partial degradation) while implanted and in service.
Malfunctions without	The condition when a device is found to have “malfunctioned”, as defined above, in a manner that did

Compromised Therapy	not compromise pacing or defibrillation therapy while implanted and in service. Therapy is not compromised as long as the critical patient-protective pacing and defibrillation therapies are available.
Normal Battery Depletion	For pulse generators, the condition when: (i) A device is returned with no associated complaint and the device has reached its elective replacement indicator(s) with implant time that meets or exceeds the nominal (50 percentile) *predicted longevity* at default (labelled) settings[(a)], or (ii) A device is returned and the device has reached its elective replacement indicator(s) with implant time exceeding 75% of the *expected longevity*[(a)] using the longevity calculation tool available at the time of product introduction, calculated using the device's actual use conditions and settings
Premature battery depletion	For pulse generators, the condition when a device is returned and confirmed to have depleted the battery in a time period less than normal battery depletion

(a) As defined by the manufacturer; variation exists between device models and companies

Despite the industry standard for this type of reporting, the requirement for analysis to be based on returned devices data may not be representative of true malfunction or device survival due to bias relating to under-reporting. Furthermore, data may not be consistently captured across manufacturers depending on how proactive different companies are in requesting devices to be returned for analysis. There are also inherent differences in the product labelling/default settings used to define "normal battery survival" between manufacturers and device models. As a consequence, results may not be comparable across manufacturers.

We have chosen not to present raw data on device malfunctions due to the bias for under-reporting and further bias from external factors such as the time interval over which data is collected (e.g., longer follow-up for older generation models). Instead we include in section 7.6.1 below a summary of device survival results compared by

device model for probability of device survival including normal battery depletion plus malfunctions and probability of device survival including malfunctions only.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

The present review was focused on CRT-D devices. The studies provided results: 1) exclusively on CRT-D implanted patients; 2) in form of pre-planned subgroup analyses with at least one group restricted to CRT-D devices only. In cases like those shown in point 2, results on CRT-D patients were reported as main findings.

The table below lists the subgroup analyses conducted:

Study name	Subgroup analysis
Alam 2016[15]	Unpublished analysis stratified by BSC models[(a)]
von Gunten 2016[19]	Analysis stratified by device type and generation: VVI-ICDs implanted before 2006; VVI-ICDs implanted after 2006; DDD-ICDs implanted before 2006; DDD-ICDs implanted after 2006; CRT-Ds implanted before 2006 (used as principal analysis); CRT-Ds implanted after 2006 (used as principal analysis)
von Gunten 2016[19]	Analysis of battery survival rates by model type (subgroup analysis for ENDURALIFE-powered/COGNIS devices in article supplementary material)
Landolina 2015[17]	Analysis stratified by generation: early generation; recent generation

(a) Personal communication from Dr Saba, May 2016

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each

Not applicable due to the non-randomised (and predominantly retrospective) fashion of all the studies and setting of analysis.

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Explicit information regarding patients lost to follow-up, withdrawing, or censored in survival analyses for any other reason, was found in von Gunten 2015[19] and Lau 2015[18]: implantable cardioverter defibrillator replacements due to normal battery depletion were considered failure events, while any other (non-depletion) replacement event was censored.

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7 Critical appraisal of randomised control trials

Removed; not relevant

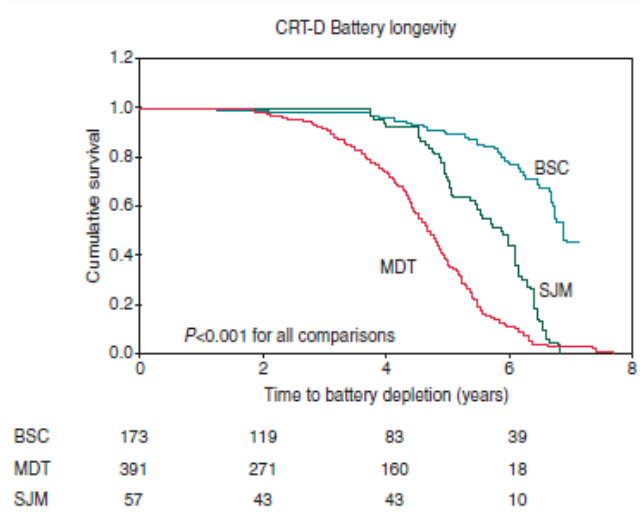
Table B8 Critical appraisal of observational studies - See Appendix 4 for full details and rationale for responses

Study name	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	Are the results precise (for example, in terms of confidence interval and p values)?
Alam 2016[15]	Yes	Yes	Yes	Yes	Yes	No	Yes
Ellis 2016[16]	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear
Landolina 2015[17]	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
Lau 2015[18]	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes
von Gunten 2015[19]	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes
Alam 2014[20]	Yes	Yes	Yes	Yes	Yes	No	Yes
Williams 2014[21]	Yes	Yes	Yes	Yes	Yes	Not clear	Yes

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B9.1 Outcomes from published studies - Alam 2016

Study name			Alam 2016[15]
Size of study groups		**Treatment**	Boston Scientific (173) ***of which ENDURALIFE-powered (71% - from Alam 2014[20])***
		Control	• Medtronic (391) • St. Jude (57)
Study duration		**Time unit**	• Mean follow-up of 3.4 (SD=±2.1) years • Maximum observation period of 95 months
Type of analysis		**Intention-to - treat/per protocol**	All patients entering the study were evaluated
Outcome 1: Rate of device replacement	**Outcome**	**Name**	Rate of device replacement for battery reaching ERI[(a)]
		Unit	Percentage
	Effect size	**Value**	• Boston Scientific=16.0% • St. Jude=53.0% • Medtronic=51.0%
		95% CI	Not reported
	Statistical test	**Type**	Chi-square
		P value	P<0.0010
Outcome 2: Time to battery depletion	**Outcome**	**Name**	Time to battery depletion
		Unit	HR
	Effect size	**Value**	• Boston Scientific vs Medtronic=0.15 • Boston Scientific vs St. Jude=0.28 • St. Jude vs Medtronic=0.46 
		95% CI	• Boston Scientific vs Medtronic=(0.10, 0.22) • Boston Scientific vs St. Jude=(0.16, 0.48) • St. Jude vs Medtronic=(0.31, 0.68)
	Statistical	**Type**	Log-rank

<table>
<tr><td></td><td>test</td><td>P value</td><td>P<0.0010</td></tr>
<tr><td rowspan="4">Outcome 3: Adjusted time to battery depletion</td><td rowspan="2">Outcome</td><td>Name</td><td>Time to battery depletion adjusted for unbalanced electrical pacing parameters between devices from different manufacturers</td></tr>
<tr><td>Unit</td><td>HR</td></tr>
<tr><td rowspan="2">Effect size</td><td>Value</td><td>• Boston Scientific vs Medtronic=0.11
• Boston Scientific vs St. Jude=0.25
• St. Jude vs Medtronic=0.36</td></tr>
<tr><td>95% CI</td><td>• Boston Scientific vs Medtronic=(0.07, 0.16)
• Boston Scientific vs St. Jude=(0.13, 0.47)
• St. Jude vs Medtronic=(0.24, 0.54)</td></tr>
<tr><td rowspan="2">Statistical test</td><td>Type</td><td>Log-rank</td></tr>
<tr><td>P value</td><td>P<0.0010</td></tr>
<tr><td rowspan="5">Outcome 4: Cumulative survival at the end of each year stratified by BSC models</td><td rowspan="2">Outcome</td><td>Name</td><td>Cumulative survival at the end of each year stratified by BSC models[b]</td></tr>
<tr><td>Unit</td><td>Percentage</td></tr>
<tr><td rowspan="2">Effect size</td><td>Value</td><td>
<table>
<tr><td></td><td colspan="7">Year</td></tr>
<tr><td>Model</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr>
<tr><td>Cognis (n=122)</td><td>100%</td><td>99%</td><td>97%</td><td>96%</td><td>96%</td><td>90%</td><td>70%</td></tr>
<tr><td>Livian (n=37)</td><td>100%</td><td>96%</td><td>91%</td><td>86%</td><td>61%</td><td>37%</td><td>0%</td></tr>
<tr><td>Renewal 3RF (n=14)</td><td>100%</td><td>100%</td><td>100%</td><td>100%</td><td>80%</td><td>20%</td><td>0%</td></tr>
</table>
</td></tr>
<tr><td>95% CI</td><td>Not reported</td></tr>
<tr><td rowspan="2">Statistical test</td><td>Type</td><td>Not reported</td></tr>
<tr><td>P value</td><td>Not reported</td></tr>
</table>

(a) Alam 2014 reports preliminary results on this outcome (median follow-up=2.7 in Alam 2014; median follow-up=3.4 in Alam 2016).

(b) Results from unpublished analysis; Personal communication from Dr Saba, May 2016.

Table B9.2 Outcomes from published studies - Ellis 2016

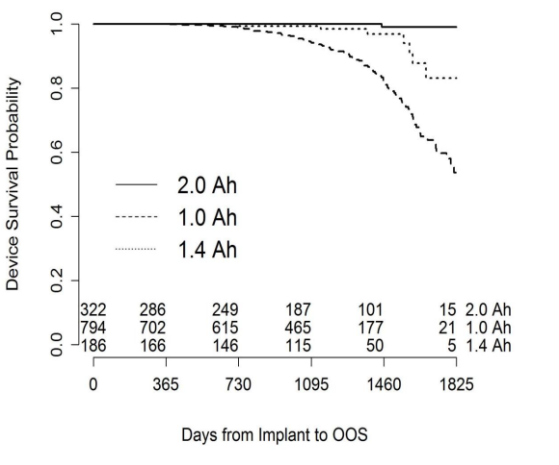
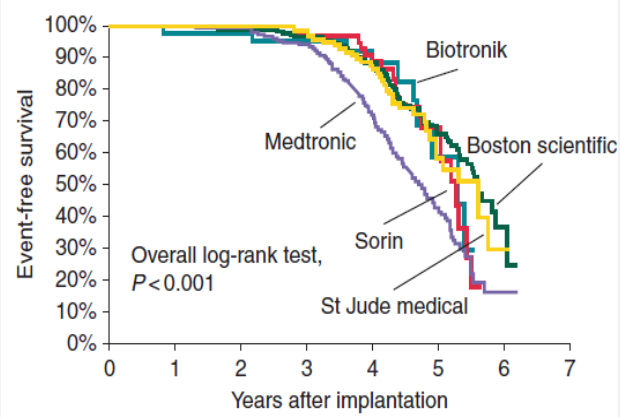
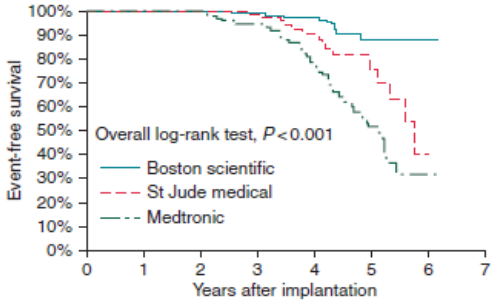
Study name			Ellis 2016[16]
Size of study groups		**Treatment**	2.0 Ah Boston Scientific (N=322) ***of which ENDURALIFE-powered (N=312, 97%)***
		Control	• 1.0 Ah Medtronic (N=794) • 1.4 Ah St. Jude (N=186)
Study duration		**Time unit**	• Mean follow-up of 3.0 years • Maximum observation period around 77 months
Type of analysis		**Intention-to - treat/per protocol**	All the patients entering the study were evaluated
Outcome 1: Proportion of batteries reaching ERI	**Outcome**	**Name**	Proportion of batteries reaching ERI
		Unit	Percentage
	Effect size	**Value**	• 13.5% of 1.0 Ah devices • 3.8% of 1.4 Ah devices • 0.3% of 2.0 Ah devices 
		95% CI	Not reported
	Statistical test	**Type**	Not reported
		P value	Not reported
Other outcome: Univariate models	**Outcome**	**Name**	Univariate models
		Unit	OR
	Effect size	**Value**	Significant predictors: • Manufacturer (Medtronic 1.0 Ah vs Boston Scientific 2.0 Ah and St. Jude 1.4 Ah, OR=9.73) • LV impedance (>1,000 vs ≤500 ohms, OR=0.38)
		95% CI	• (4.70, 20.15) for Manufacturer • (0.20, 0.71) for LV impedance
	Statistical test	**Type**	F-test for both Manufacturer and LV impedance
		P value	• P<0.0001 for manufacturer • P=0.0025 for LV impedance

Table B9.3 Outcomes from published studies - Landolina 2015

Study name			Landolina 2015[17]
Size of study groups		**Treatment**	Boston Scientific (N=291 RG; N=317 EG) ***of which ENDURALIFE-powered (N=317, 100% of RG devices)***
		Control	• Biotronik (N=20 RG; N=29 EG) • Medtronic (N=532 RG; N=266 EG) • Sorin (N=69 RG; N=30 EG) • St. Jude (N=106 RG; N=66 EG)
Study duration		**Time unit**	• Median follow-up of 43 months • Maximum observation around 63 months
Type of analysis		**Intention-to-treat/per protocol**	All the patients entering the study were evaluated
Outcome 1: Device survival	**Outcome**	**Name**	Device survival (overall CRT-D population)
		Unit	Percentage
	Effect size	**Value**	Ranged from 42.0% for Medtronic CRT-D to 66.0% for Boston Scientific **Overall population** 
		95% CI	Not reported
	Statistical test	**Type**	Log-rank
		P value	P<0.0010

Outcome 2: Device survival (recent generation devices)	**Outcome**	**Name**	Device survival (recent generation devices)
		Unit	Percentage
	Effect size	**Value**	• Boston Scientific=88.0% • St. Jude=75.0% • Medtronic=52.0% **Recent generation subgroup** 
		95% CI	Not reported
	Statistical test	**Type**	Log-rank
		P value	P<0.0100
Other outcome 1: Univariate models	**Outcome**	**Name**	Univariate models
		Unit	HR
	Effect size	**Value**	Significant predictors: • Boston Scientific (HR=0.54) • Recent generation (HR=0.50) • Battery chemistry: Li/CFx-SVO (HR=0.42) • Battery chemistry: Li/MnO2 (HR=0.20) • High LV lead output (HR=1.74) • Unipolar LV lead (HR=1.71) • True-bipolar right ventricular lead (HR=0.47)
		95% CI	• (0.43, 0.67) for Boston Scientific • (0.40, 0.61) for Recent generation • (0.24, 0.72) for Battery chemistry: Li/CFx-SVO • (0.13, 0.33) for Battery chemistry: Li/MnO2 • (1.39, 2.18) for High LV lead output • (1.37, 2.13) for Unipolar LV lead • (1.21, 1.79) for True-bipolar right ventricular lead
	Statistical test	**Type**	F-test
		P value	• P<0.0010 for Boston Scientific • P<0.0010 for Recent generation • P=0.0020 for Battery chemistry: Li/CFx-SVO • P<0.0010 for Battery chemistry: Li/MnO2 • P<0.0010 for High LV lead output • P<0.0010 for Unipolar LV lead • P<0.0010 for True-bipolar right ventricular lead
Other outcome 2: Multivariate models	**Outcome**	**Name**	Multivariate models
		Unit	HR
	Effect size	**Value**	Significant Predictors: • Boston Scientific (HR=0.64) • Recent generation (HR=0.57) • Battery chemistry: Li/CFx-SVO (HR=0.28) • Battery chemistry: Li/MnO2 (HR=0.37) • High LV lead output (HR=1.96) • Unipolar LV lead (HR=1.58)
		95% CI	• (0.47, 0.89) for Boston Scientific • (0.45, 0.72) for Recent generation

			• (0.16, 0.50) for Battery chemistry: Li/CFx-SVO • (0.22, 0.64) for Battery chemistry: Li/MnO2 • (1.57, 2.46) for High LV lead output • (1.25, 2.01) for Unipolar LV lead
	Statistical test	**Type**	F-test
		P value	• P=0.0080 for Boston Scientific • P<0.0010 for Recent generation • P<0.0010 for Battery chemistry: Li/CFx-SVO • P<0.0010 for Battery chemistry: Li/MnO2 • P<0.0010 for High LV lead output • P<0.0010 for Unipolar LV lead

Table B9.4 Outcomes from published studies - Lau 2015

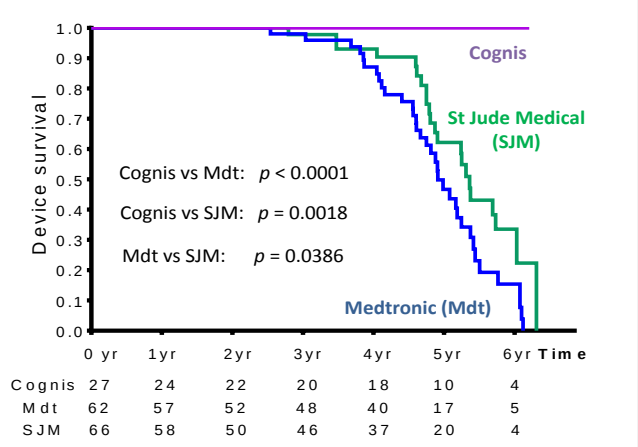
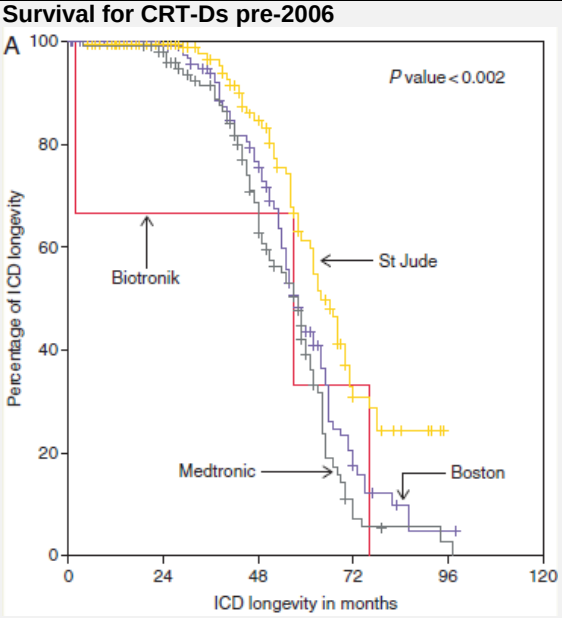
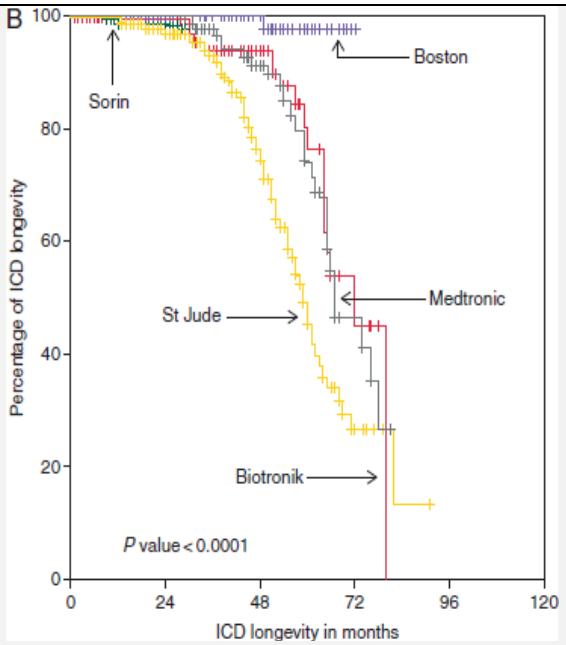
Study name			Lau 2015[18]
Size of study groups		**Treatment**	Boston scientific (27) ***of which ENDURALIFE-powered (N=27, 100%)***
		Control	• St. Jude (66) • Medtronic (62)
Study duration		**Time unit**	Not reported
Type of analysis		**Intention-to-treat/per protocol**	All patients entering the study were evaluated
Outcome1: 6-y survival	**Outcome**	**Name**	6-year device survival to ERI
		Unit	Percentage
	Effect size	**Value**	• Boston Scientific=100.0% • St. Jude/Medtronic=0.0% 
		95% CI	Not reported
	Statistical test	**Type**	Log-rank
		P value	Pairwise comparisons: • Boston Scientific vs St. Jude: P=0.0018 • Boston Scientific vs Medtronic: P<0.0001 • St. Jude vs Medtronic: P=0.0386

Table B9.5 Outcomes from published studies - von Gunten 2015

Study name			von Gunten 2015[19]
Size of study groups		**Treatment**	• Boston Scientific (N=259 CRT) ***of which ENDURALIFE -powered (N=100, 39%)***
		Control	• Biotronik (N=228 CRT) • Intermedics (N=0 CRT) • Medtronic (N=267 CRT) • St. Jude (N=526 CRT) • Sorin (N=4 CRT)
Study duration		**Time unit**	• Median follow-up 53 months[(a)] • Maximum observation 63 months[(a)]
Type of analysis		**Intention-to-treat/per protocol**	All patients entering the study were evaluated
Outcome 1: Proportion of battery survival pre- and post-2006	**Outcome**	**Name**	Proportion of battery survival (longevity) pre- and post-2006
		Unit	Percentage
	Effect size	**Value**	**Survival for CRT-Ds pre-2006**  **Survival for CRT-Ds post-2006**

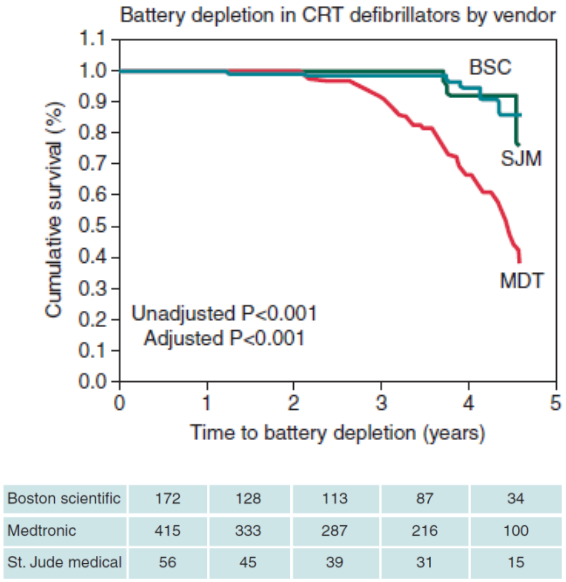
<table>
<tr><td></td><td></td><td></td><td> 
</td></tr>
<tr><td></td><td></td><td>95% CI</td><td>Not reported</td></tr>
<tr><td></td><td>Statistical test</td><td>Type</td><td>Log-rank</td></tr>
<tr><td></td><td></td><td>P value</td><td>• P<0.0020 for devices implanted before 2006
• P<0.0001 for devices implanted after 2006</td></tr>
<tr><td>Outcome 2: 5-year battery survival for CRT-Ds</td><td>Outcome</td><td>Name</td><td>5-year battery survival (longevity) for CRT-Ds</td></tr>
<tr><td></td><td></td><td>Unit</td><td>Percentage</td></tr>
<tr><td></td><td>Effect size</td><td>Value</td><td>• Boston=97.6%
• Medtronic=74.1%
• St. Jude Medical=45.3%</td></tr>
<tr><td></td><td></td><td>95% CI</td><td>Not reported</td></tr>
<tr><td></td><td>Statistical test</td><td>Type</td><td>Log-rank</td></tr>
<tr><td></td><td></td><td>P value</td><td>P≤0.0010</td></tr>
<tr><td>Outcome 3: 6-year battery survival for CRT-Ds</td><td>Outcome</td><td>Name</td><td>6-year battery survival (longevity) for CRT-Ds</td></tr>
<tr><td></td><td></td><td>Unit</td><td>Percentage</td></tr>
<tr><td></td><td>Effect size</td><td>Value</td><td>• Boston=97.6%
• Medtronic=46.3%
• St. Jude Medical=26.5%</td></tr>
<tr><td></td><td></td><td>95% CI</td><td>Not reported</td></tr>
<tr><td></td><td>Statistical test</td><td>Type</td><td>Log-rank</td></tr>
<tr><td></td><td></td><td>P value</td><td>P≤0.0010</td></tr>
<tr><td>Outcome 4: 4-year battery survival for CRT-Ds, by model**</td><td>Outcome</td><td>Name</td><td>4-year battery survival (longevity) for CRT-Ds, by model[(b)]</td></tr>
<tr><td></td><td></td><td>Unit</td><td>Percentage</td></tr>
<tr><td></td><td>Effect size</td><td>Value</td><td><table>
<tr><th>Model</th><th>Result</th></tr>
<tr><td>Boston Scientific Cognis (ENDURALIFE-powered)</td><td>97.5%</td></tr>
<tr><td>Biotronik Lumax 540 HF-T</td><td>95.0%</td></tr>
<tr><td>Medtronic Concerto C 174</td><td>93.4%</td></tr>
<tr><td>St. Jude Medical Promote RF 3213</td><td>91.3%</td></tr>
<tr><td>Medtronic InSync III Marquis 7279</td><td>57.1%</td></tr>
</table></td></tr>
<tr><td></td><td></td><td>95% CI</td><td>Not reported</td></tr>
</table>

	Statistical test	**Type**	Not reported
		P value	Not reported

(a) Referred to the entire cohort=CRT-D+ICD implanted patients.

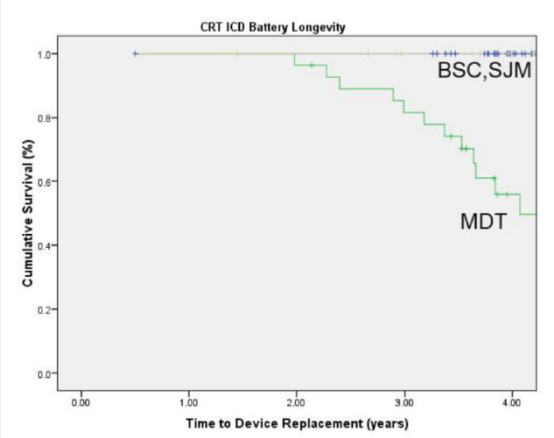
(b) Findings shown in the Supplementary Material (Europace online).

Table B9.6 Outcomes from published studies – Alam 2014

Study name			Alam 2014[20]
Size of study groups		**Treatment**	Boston Scientific (N=173) ***of which ENDURALIFE-powered (N=122, 71%)***
		Control	• Medtronic (N=416) • St. Jude (N=57)
Study duration		**Time unit**	• Mean follow-up of 2.7 (SD=±1.5) years • Maximum observation period of 63 months
Type of analysis		**Intention-to - treat/per protocol**	All the patients entering the study were evaluated
Outcome 1: Rate of device replacement	**Outcome**	**Name**	Rate of device replacement for battery reaching ERI
		Unit	Percentage
	Effect size	**Value**	• Boston Scientific=4.0% • St. Jude=7.0% • Medtronic=25.0%
		95% CI	Not reported
	Statistical test	**Type**	Chi-square
		P value	P<0.0010
Outcome 2: 4-year survival	**Outcome**	**Name**	4-year survival rate of device battery
		Unit	Percentage
	Effect size	**Value**	• Boston Scientific=94.0% • St. Jude=92.0% • Medtronic=67.0%  Boston scientific 172 128 113 87 34 Medtronic 415 333 287 216 100 St. Jude medical 56 45 39 31 15
		95% CI	Not reported
	Statistical test	**Type**	Log-rank
		P value	P<0.0010
One ..	**Outcome**	**Name**	Cox model

		Unit	OR
	Effect size	**Value**	Significant predictors: • Manufacturer (Medtronic vs other, OR=6.27) • LV output (OR=1.97)
		95% CI	• (2.53, 15.52) for Manufacturer • (1.64, 2.37) for LV
	Statistical test	**Type**	Chi-square for both Manufacturer and LV output
		P value	P<0.0010 for both Manufacturer and LV output

Table B9.7 Outcomes from published studies - Williams 2014

Study name			Williams 2014[21]
Size of study groups		**Treatment**	Boston Scientific (N=53) ***of which ENDURALIFE -powered (N=51, 96%)***[(a)]
		Control	• Medtronic (N=28) • St. Jude (N=10)
Study duration		**Time unit**	Average follow-up 4 ± 0.8 years
Type of analysis		**Intention-to-treat/per protocol**	All the patients entering the study were evaluated
Outcome1: Rate of device replacement for battery reaching ERI	**Outcome**	**Name**	Rate of device replacement for battery reaching ERI
		Unit	Percentage
	Effect size	**Value**	• Boston Scientific=1.9% • Medtronic=50.0% • St. Jude=10.0% 
		95% CI	Not reported
	Statistical test	**Type**	Log-rank
		P value	P<0.0010

Other outcome: Cox model	**Outcome**	**Name**	Cox model
	Effect size	**Value**	Patients reaching ERI had higher RV and LV output and RV pulse width
		95% CI	Not reported
	Statistical test	**Type**	Not reported
		P value	Not reported

(a) Personal communication from Dr Williams, May 2016

Unpublished Studies

Table B9 below summarises the results from Product Performance Reports. We have included this information to illustrate the significance of battery survival versus device survival as outlined in the statement of the decision problem in the scope.[4]

Table B9 Summary of results of the unpublished evidence listed in Table B4 and considered for the present review

	CRT-D devices	US Registered Implants[(a)]	Interval	Survival Probability - normal battery depletion + malfunctions (%)	Statistical significance	Survival Probability - malfunctions only (exc. normal battery depletion) (%)	Statistical significance
Biotronik[22]	Ilesto 7 HF-T	3,410	12 months	99.9	CI 95% ± 0.2	100.0	-
	Lumax 340 HF/HF-T	5,310	72 months	73.4	CI 95% ± 2.0	99.9	CI 95% ± 0.1
	Lumax 540 HF-T	8,660	60 months	82.3	CI 95% ± 3.4	99.7	CI 95% ± 0.3
	Lumax 740 HF-T	3,410	24 months	99.7	CI 95% ± 0.3	99.9	CI 95% ± 0.1
Boston Scientific[23]	Autogen	n/a	-	-	-	-	-
	Dynagen/Inogen/Origen[(e)]	15,000	18 months	99.89	CI 95% ± 0.1	99.93	CI 95% -0.1/+0.0
	Incepta/Energen/Punctua[(f)]	51,000	47 months	99.09	CI 95% -0.3/+0.2	99.69	CI 95% -0.2/+0.1
	Cognis[(b)(g)]	75,000	84 months	87.16	n/a	94.84	n/a
Medtronic[24]	InSync Sentry Model 7299	31,168	69 months	0.2	n/a	98.8	n/a
	InSync Maximo Model 7304	18,962	66 months	1.3	n/a	99.0	n/a
	Concerto Models C154DWK, C164AWK, C174AWK	81,410	80 months	2.3	n/a	96.5	n/a
	Consulta Models D204TRM, D224TRK, D234TRK	67,858	74 months	18.6	n/a	98.5	n/a

	Maximo II	[redacted]	74 months	26.4	n/a	98.5	n/a
	Concerto II	30,164	67 months	41.2	n/a	99.1	n/a
	D3xxTRx[(c)]	[redacted]	51 months	82.1	n/a	99.8%	n/a
	Blackwell[(d)]	81,820	30 months	99.7	n/a	100.0	-
Sorin[25]	Alto	*Consolidated results not reported; results presented for various advisory groups only*					
	Intensia	n/a	12 months	*Quantitative data not reported; graphical representation only*		100.00	-
	Ovatio	n/a	120 months			99.78	CI 95% -0.22/+0.11
	Paradym	n/a	84 months			99.82	CI 95% -0.16/+0.08
	Paradym 2	n/a	24 months			100.0	-
	Paradym RF	n/a	48 months			99.88	CI 95% -0.17/+0.07
St Jude Medical[26]	Quadra Assura CD3365-40Q	28,951	28 months	99.70	SE ± 0.05	99.80	SE ± 0.04
	Quadra Assura **CD3365-40C**	5,757	26 months	99.43	SE ± 0.16	99.57	SE ± 0.15
	Unify Assura **CD3357-40Q**	5,790	25 months	99.61	SE ± 0.11	99.77	SE ± 0.08
	Unify Assura **CD3357-40C**	10,958	27 months	99.67	SE ± 0.15	99.69	SE ± 0.15

	Quadra Assura **D3265-40Q**	13,523	42 months	99.46	SE ± 0.10	99.82	SE ± 0.05
	Quadra Assura **CD3265-40**	4,020	40 months	99.61	SE ± 0.11	99.68	SE ± 0.10
	Unify Assura **CD3257-40Q**	2,710	39 months	98.89	SE ± 0.31	99.89	SE ± 0.08
	Unify Assura **CD3257-40**	6,728	41 months	98.63	SE ± 0.22	99.57	SE ± 0.11
	Unify Quadra **CD3249-40Q**	8,931	48 months	98.80	SE ± 0.18	99.77	SE ± 0.07
	Unify Quadra **CD3249-40**	2,520	47 months	99.45	SE ± 0.18	99.92	SE ± 0.06
	Unify **CD3231-40Q**	18,982	67 months	92.12	SE ± 0.36	97.97	SE ± 0.18
	Unify **CD3231-40**	20,470	67 months	88.36	SE ± 0.56	98.86	SE ± 0.11
	Promote + **Model CD3211-36Q**	6,900	75 months	56.28%	SE ± 1.11	98.14	SE ± 0.23
	Promote + **Model CD3211-36**	8,645	78 months	42.51%	SE ± 1.07	98.17	SE ± 0.22
	Promote RF **Model 3207-36**	24,001	95 months	30.55%	SE ± 0.59	97.58	SE ± 0.16
	Atlas + HF **Model V-343**	18,777	121 months	9.65%	SE ± 0.31	97.70	SE ± 0.26

(a) Includes devices which have been explanted or are otherwise out of service

(b) Consolidated survival data inclusive of advisory populations; not included in published Product Performance Report

(c) Includes Protecta, Protecta XT, Cardia and Egida CRT-D devices

(d) Includes Viva S, Viva Quad S, Viva XT, Viva Quad XT, Viva Quad C, Brava and Brava Quad CRT-D devices

(e) Models G050/G051/G056/G058/G140/G141/G146/G148/G150/G151/G154/G156/G158

(f) Models N050/N051/N052/N053/N140/N141/N142/N143/N160/N161/N162/N163/N164/N165/P052/P053/P142/P143/P162/P163/P165

(g) Models N106/N107/N108/N118/N119/N120/P106/P107/P108

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

Not applicable. All the screened evidence on longevity, adverse events and patients' outcomes came from non-randomised studies.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.
For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Improved longevity has been demonstrated to reduce the need for replacement procedures.[28] Considering these avoidable replacement procedures, we performed a second systematic literature review to understand the burden of these replacement procedures focusing on relevant published studies which:

(i) discussed the incidence of complications due to replacement procedures for any reason

(ii) reported outcomes relating to patient quality of life or satisfaction in the context of replacement device procedures

A systematic approach to identifying clinical and background literature was followed, analysing the Pubmed library. Please see Table B10 below for selection criteria used to identify relevant published studies. Additionally, hand-searching of internal company documentation was performed in order to find studies not indexed. Please refer to PRISMA diagram (Figure B2) for the algorithm of search.

This review was derived from a search conducted on 4th May 2016. The studies identified in this second literature search were independently assessed by a reviewer, in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were revolved by a second reviewer. Data was extracted from

eligible publications into a pre-defined table by a reviewer (see Appendix 5 to obtain exact details of the search strategy). Please refer to:

- Table B11 to obtain a full list and details of methodology of relevant studies
- Table B12 for a summary of the critical appraisal of relevant studies
- Table B13 for the results of the relevant studies

The clinical studies identified in section 7.3 contained no reports of adverse events relating to replacement procedures.

No RCTs or unpublished studies relevant to the submission were identified.

Table B10 Selection criteria used for published studies – Outcome search

Inclusion criteria	
Population	Patients implanted with CRT-Ds
Interventions	Patients undergoing CRT-D replacement
Outcomes	Adverse events (including death); patients' quality of life and satisfaction; infection/complication rate associated with replacement
Study design	• All studies (conducted in experimental or observational setting) evaluating the risks associated with CRT-D replacement procedures (including a comparison with risks associated with de novo procedures when available) • Systematic reviews and meta-analyses analysing patients' outcomes related to CRT-D replacement procedures (including a comparison with risks associated with de novo procedures when available)
Language restrictions	English language only
Other restrictions	Full text or abstract available
Search dates	-
Exclusion criteria	
Population	Patients implanted exclusively with ICDs (i.e. ICD-VR, ICD-DR, not CRT-Ds)
Interventions	-
Outcomes	-
Study design	Editorials
Language restrictions	English language only
Other restrictions	Full text or abstract available
Search dates	-

Figure B2 PRISMA flow diagram for outcome search

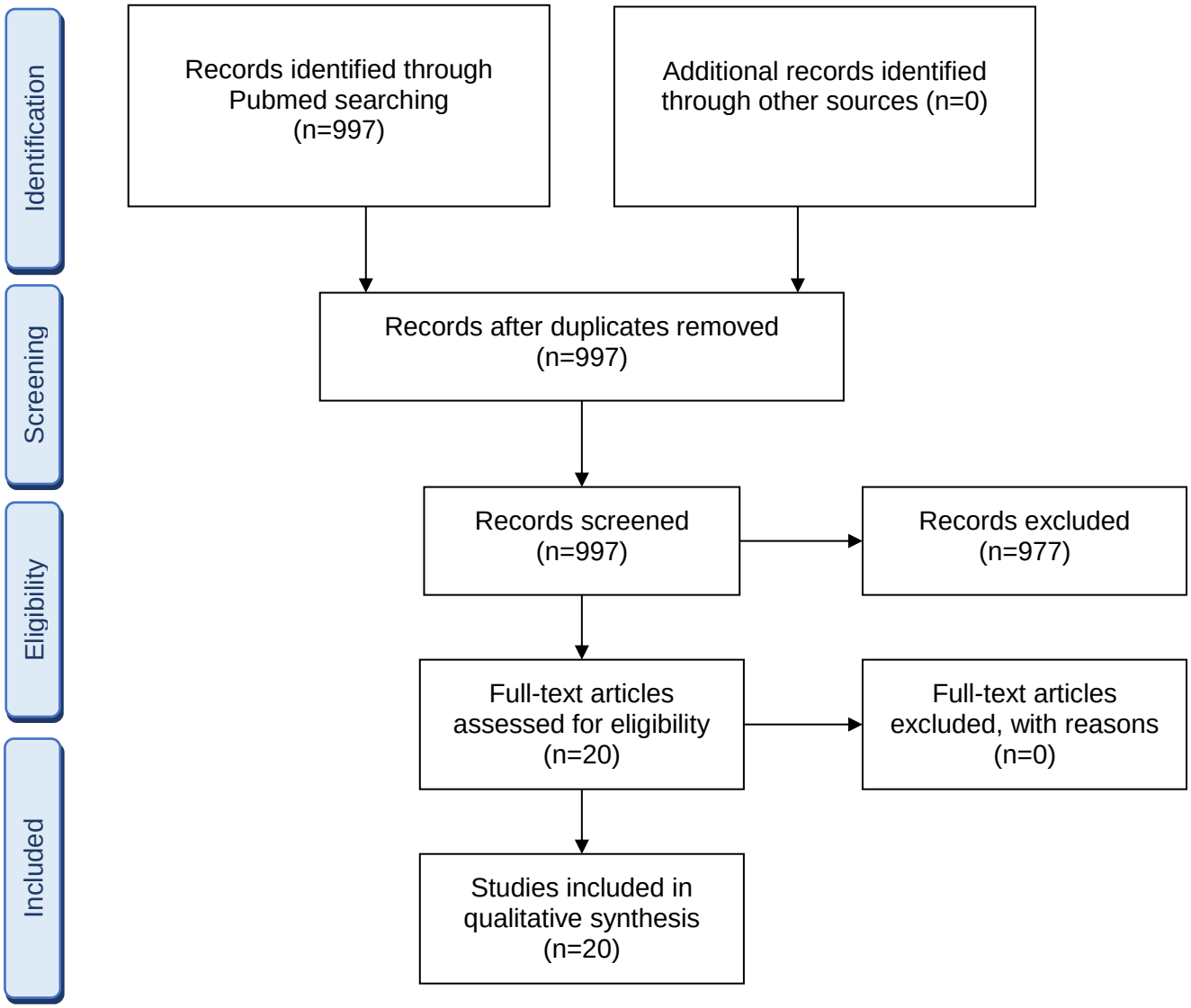


Table B11 List and methodology of relevant published studies

Study reference	Study title	Study Design & location	Population	Sample size	Objective	Outcomes reported
Lewis 2016[(b)29]	Estimating the risks and benefits of implantable cardioverter defibrillator generator replacement: a systematic review	• Review of N=17 studies • Sources: Cochrane DB; DARE; CENTRAL; MEDLINE; EMBASE; PsycINFO; CINAHL	Patients implanted with ICD, undergoing pulse generator replacement	N=316,527 patients (Pooled population across the 17 studies)	To synthesise the evidence on risks, benefits, and costs related to ICD/CRT-D replacement	• Median rate of major complications • Median rate of minor complications
Nichols 2016[30]	Incidence and costs related to lead damage occurring within the first year after a cardiac implantable electronic device replacement procedure	• Registry claim data analysis • Retrospective • Multi-centre (# not reported) • 1-year follow-up • Enrolment period: 2010–2012	Patients implanted with PM, ICD, CTR-D, undergoing generator replacement	N=45,252 patients	To estimate the incidence and costs associated with transvenous lead damage following cardiac implantable electronic device replacement	Lead damage rates related to replacement
Polyzos 2015[(c)31]	Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis	• Review of N=60 studies • Sources: PubMed; Scopus; Web of Science databases	Patients undergoing de novo implantation or replacement/revision/upgrade of a PPM, ICD, CRT-D	N=233,184 patients (Pooled population across the 60 studies)	To examine potential risk factors for CIED infection	Procedure and device-related risk factors for device-related infection
Zeitler 2015[(a)32]	Complications from prophylactic replacement of cardiac implantable electronic device	• Review of N=7 studies • Sources: MEDLINE and	Patients implanted with cardiac implantable	N=1,435 patients (Pooled population	To estimate complication rates for recalled CIED generators replaced	Rates of: • Overall complication • Mortality

Study reference	Study title	Study Design & location	Population	Sample size	Objective	Outcomes reported
	generators in response to United States Food and Drug Administration recall: a systematic review and meta-analysis	Cochrane Controlled Trials Register	electronic devices (CIEDs) undergoing prophylactic replacement	across the 7 studies)	prophylactically	• Reoperation/pocket revision
Lovelock 2014[33]	Generator replacement is associated with an increased rate of ICD lead alerts	• Retrospective • Multi-centre (# not reported) • 37-months follow-up (average) • Enrolment period: as of 2006	Patients undergoing Boston Scientific ICD and CRT-D generator exchange (ALTITUDE database)	• Patient cohort: N=60,219 patients • Analysis cohort: N=7,458 patients with generator exchange	To assess the effect of ICD/CRT-D generator exchange on the rate of lead alerts	• 1-year performance of the ICD lead after elective ICD generator replacement • Predictors of ICD lead alert rate
Prutkin 2014[34]	Rates of and factors associated with infection in 200 909 medicare implantable cardioverter-defibrillator implants results from the national cardiovascular data registry	• Registry claim data analysis • Retrospective • Multi-centre (1,348 centres) • 6-months follow-up • Enrolment period: 2006-2009	Patients undergoing ICD/CRT-D de novo implantation or replacement	• Patient cohort: N=200,909 patients • Analysis cohort: (N=3,390 patients)	To determine the rate and predictors of ICD-related infection	• 6-month infection rates • Predictor of risk of infection
Kramer 2013[35]	Characteristics and outcomes of patients receiving new and replacement implantable cardioverter-defibrillators: results from the NCDR	• Prospective • Multi-centre (1,489 centres) • Follow-up for the replacement and de novo ICD/CRT-D patients: 2.04 years and 2.54	Patients undergoing ICD/CRT-D de novo implantation or replacement	N=463,978 patients	To determine procedural risks and survival of patients receiving replacement versus de novo ICDs/CRT-Ds	• Complication rates • Median survival • 1-year mortality • 3-year mortality

Study reference	Study title	Study Design & location	Population	Sample size	Objective	Outcomes reported
		years, respectively • Enrolment period: January 2005-March 2010				
Palmisano 2013[36]	Rate, causes, and impact on patient outcome of implantable device complications requiring surgical revision: large population survey from two centres in Italy	• Retrospective • Multi-centre (2 centres) • 27-months follow-up • Enrolment period: January 2006-March 2011	Patients undergoing PM, ICD, CRT-D de novo implantation or replacement procedures	• N=2,648 patients • N=2,671 procedures (1511 de novo, 1034 replacements, 126 upgrades)	To analyse the rate and nature of complications per device type and type of initial procedure	• Complication rates per procedure-year • Complication-free survival, by type of initial procedure
Lovelock 2012[37]	Generator exchange is associated with an increased rate of sprint fidelis lead failure	• Prospective, matched control analysis • Multi-centre (2 centres) • 60.2-months follow-up (average) • Implantation period: September 2004-October 200	Patients implanted with Medtronic Sprint Fidelis ICD leads	• Patient cohort: N=1,366 patients • Analysis cohort N=222 patients (72 patients with generator exchange vs 150 matched controls)	To assess the effect of implantable cardioverter-defibrillator generator exchange on the rate of Fidelis lead failure	1-year lead damage rates
Uslan 2012[38]	Cardiovascular implantable electronic device replacement infections and prevention: results from the REPLACE registry	• Prospective • Multi-centre (72 centres) • 6-months follow-up • Enrolment period: not reported	Patients undergoing CIED replacement	N=1,744 patients	To analyse the incidence of CIED-related infections and determine the main risk factors	Infection rates
Krahn	Predictors of short-term	• Prospective	Patients	1,081 patients	To identify factors	• Overall

Study reference	Study title	Study Design & location	Population	Sample size	Objective	Outcomes reported
2011[39]	complications after implantable cardioverter-defibrillator replacement results from the Ontario ICD database	• Multi-centre (18 centres) • 1.5-months follow-up • Enrolment period: February 2007-August 2009	undergoing ICD/CRT-D replacement		contributing to complications	complication rates • Complication rates associated with lead addition • Mortality
Landolina 2011[40]	Long-Term complications related to biventricular defibrillator implantation rate of surgical revisions and impact on survival: insights from the Italian clinical service database	• Prospective • Multi-centre (117 centres) • 18-months follow-up (median) • Enrolment period: 2004-2009	Patients undergoing CRT-D de novo implantation of CRT-Ds	N=3,253 patients	To quantify the frequency of invasive procedures (after initial implant) and the nature of long-term complications	• Infection rates • Predictors of risk of infection
Borleffs 2010[41]	Recurrent implantable cardioverter-defibrillator replacement is associated with an increasing risk of pocket-related complications	• Prospective • Single-centre • 38-months follow-up (average) • Enrolment period: 1992-2008	Patients undergoing ICD/CRT-D de novo implantation	2,415 patients	To evaluate the requirement for pocket-related surgical re-interventions following ICD treatment and the effect of device replacement	• Surgical re-intervention in first implant versus replacement ICD/CRT-D • Relationship between number of ICD/CRT-D replacements and the need for surgical re-intervention
Nery 2010[42]	Device-related infection among patients with pacemakers and implantable	• Retrospective • Single-centre • Follow-up: not reported	Patients implanted with PM or ICD/CRT-D	2,417 patients	To evaluate device related infection	• Infection rates • Predictors of infections

Study reference	Study title	Study Design & location	Population	Sample size	Objective	Outcomes reported
	defibrillators: incidence, risk factors, and consequences	• Enrolment period: July 2003-March 2007				
Poole 2010[43]	Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures. results from the REPLACE registry	• Prospective • Multi-centre (72 centres) • 6-months follow-up • Enrolment period: July 2007-November 2008	Patients undergoing elective PM or ICD replacement	N=1,744 patients Cohort 1 (N=1,031 replacements with lead addition) Cohort 2 (N=713 replacements with no lead addition)	To estimate major and minor infection rate	6-month rates of: • Major complication • Minor complication • Major complication by lead procedure
Costea 2008[44]	Complications associated with generator replacement in response to device advisories	• Prospective • Single-centre • 3-months follow-up • Enrolment period: January 2005-December 2005	Patients implanted with Medtronic or Guidant ICDs	• Patient cohort: N=1,039 patients • Analysis cohort: N=222 patients with device replacement	To analyse reasons for and outcomes of ICD/CRT-D and pacemaker generator changes (resulting from advisories)	Complication rates related to replacement
Gould 2008[45]	Outcome of advisory implantable cardioverter-defibrillator replacement: one-year follow-up	• Retrospective • Multi-centre (12 centres) • 1-year follow-up • Enrolment period: October 2004-	Patients undergoing ICD replacement	N=451 patients	To assess replacement-related complications	• Rates of: - Major complication - Minor complication • Predictors of

Study reference	Study title	Study Design & location	Population	Sample size	Objective	Outcomes reported
		October 2005				complication
Kapa 2007[46]	Complication risk with pulse generator change: implications when reacting to a device advisory or recall	• Retrospective • Single-centre • 2-months follow-up • Enrolment period: 2000-2005	Patient undergoing PM, ICD, CRT-D replacements indicated for either ERI or manufacturer advisory or recall	N=732 (replacements)	To assess operative complication rates	Complication rates related to replacement
Gould 2006[47]	Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories	• Retrospective • Multi-centre (17 centres) • 2.7-months follow-up • Enrolment period: October 2004-October 2005	Patient undergoing ICD replacement	N=533 patients	To determine the complication rate associated with ICD/CRT-D generator replacement	Rates of: • Major complication • Minor complication
Wild 2004[48]	Pacemakers and implantable cardioverter defibrillators. Device longevity is more important than smaller size: the patient's viewpoint	• Retrospective • Single-centre • Cross-sectional evaluation	Patients implanted with PMs and ICDs	N=151 patients	To determine drivers of patients' preference between: i) larger and longer-lasting vs ii) smaller but shorter-lasting ICDs	Proportion of patients preferring larger/smaller devices

(a) Kapa 2007, Gould 2006, Costea 2007 included in this review.

(b) Kapa 2007, Costea 2007, Borleffs 2010, Krahn 2011, Kramer 2013, Poole 2010, Prutkin 2014 included in this review.

(c) Gould 2008, Palmisano 2013, Uslan 2012, Landolina 2011, Borleffs 2010, Nery 2010, Krahn 2011.

Table B12 Critical appraisal of relevant published studies

Study name	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	Are the results precise (for example, in terms of confidence interval and p values)?
Lewis 2016[29]	Yes	Yes	Yes	Yes	Yes	Not clear as it is a review	Yes
Nichols 2016[30]	Yes	Yes	Yes	Yes	Yes	Yes[(a)]	Yes
Polyzos 2015[31]	Yes	Yes	Yes	Yes	Yes	Not clear as it is a review	Yes
Zeitler 2015[32]	Yes	Yes	Yes	Yes	Yes	Not clear as it is a review	Yes
Lovelock 2014[33]	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
Prutkin 2014[34]	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes
Kramer 2013[35]	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
Palmisano 2013[36]	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes

Study name	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	Are the results precise (for example, in terms of confidence interval and p values)?
Lovelock 2012[37]	Yes	Yes	Yes	Yes	Yes	Yes[(a)]	Yes
Uslan 2012[38]	Yes	Yes	Not clear	Yes	Yes	No	Yes
Krahn 2011[39]	Yes	Yes	Yes	Yes	Yes	Yes[(a)]	Yes
Landolina 2011[40]	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes
Borleffs 2010[41]	Yes	Yes	Yes	Yes	Yes	Yes[(a)]	Yes
Nery 2010[42]	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
Poole 2010[43]	Yes	Yes	Yes	Yes	Yes	Yes[(a)]	Yes
Costea 2008[44]	Yes	Yes	Yes	Yes	No	Yes[(a)]	Not required for the outcome evaluated

Study name	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	Are the results precise (for example, in terms of confidence interval and p values)?
Gould 2008[45]	Yes	Yes	Yes	Yes	Yes	Yes[(a)]	Yes
Kapa 2007[46]	Yes	Yes	Yes	Yes	No	Yes[(a)]	Not required for the outcome evaluated
Gould 2006[47]	Yes	Yes	Not clear	Yes	No	Not clear	Not required for the outcome evaluated
Wild 2004[48]	Yes	Yes	Yes	Yes	No	Not required (cross-sectional survey)	Yes

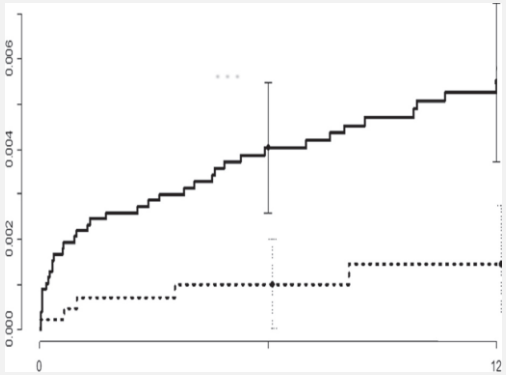
(a) Evaluation limited to patients who effectively enter the study.

7.7.2 Provide details of all important adverse events reported for each study.

Adverse events as identified in section 7.7.1 can be summarised as follows:

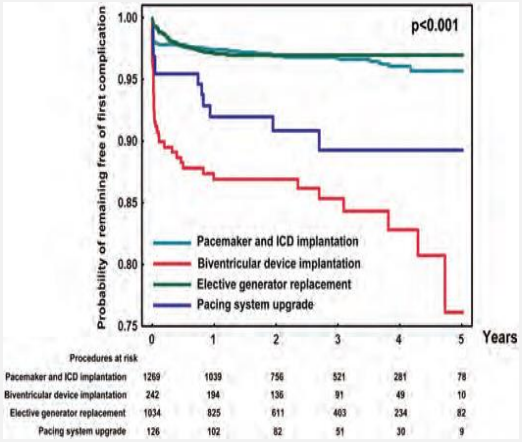
Table B13 Outcome reported across patient groups

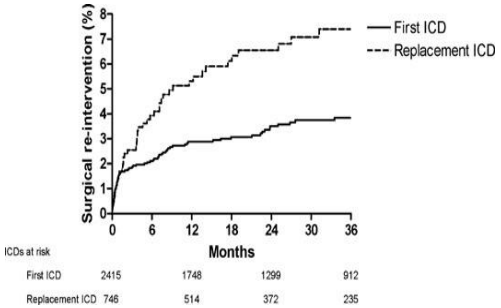
Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
Lewis 2016[29]	Median rate of major complications	No	4.05%; CI 95% (0.55, 7.37)	-	Systematic review. Rates of complications associated with ICD replacement are substantial
	Median rate of minor complications	No	3.50%; CI 95% (0.36, 7.37)	-	
Nichols 2016[30]	Lead damage rates related to replacement	No	• CRT (N=2,063)=1.94% • ICD (N=20,632)=1.27% • PM (N=22,557)=0.46%	Not applicable	Replacements are associated with a risk of lead damage within the first year. The risk is higher for CRT-Ds compared to ICDs and PMs
Polyzos 2015[31]	Procedure and device-related risk factors for device-related infection	Yes	Pooled OR for significant predictors: • post-operative haematoma=8.46 • reintervention for lead dislodgement=6.36 • device replacement/revision=1.98 • lack of antibiotic prophylaxis=0.32 • temporary pacing=2.31 • generator change=1.74 • dual-chamber system=1.45 • inexperienced operator=2.85 • abdominal generator pocket=4.01	P<0.050 (at least) for all variables reported	Device replacement/revision of CIEDs is a risk factor for infection

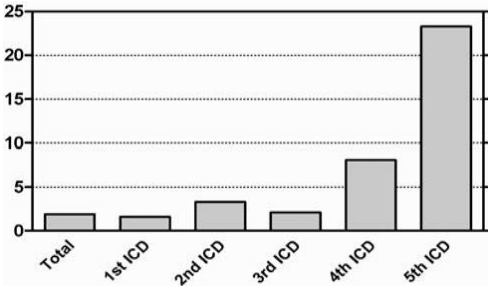
Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
Zeitler 2015[32]	Overall complications rate	No	2.60%; CI 95% (1.05, 4.46)	-	The complication risk from prophylactic replacement of CIEDs is similar to that associated to replacement for other reasons
	Mortality rate		0.47%; CI 95% (0.13, 0.91)	-	
	Reoperation/pocket revision rate		2.51%; CI 95% (0.87, 4.53)	-	
Lovelock 2014[33]	1-year performance of the ICD lead after elective ICD generator replacement	Yes		P<0.0010	Routine generator replacement is associated with a 5-fold higher risk of lead alert compared to age-matched leads without generator replacement
	Predictors of ICD lead alert rate	Yes	OR for significant predictors: • Generator replacement=5.20 • Age=1.02 • Single chamber (vs dual chamber)=2.49	P<0.0010	
Prutkin 2014[34]	6-month infection rates	No	1.7%		Replacement for device upgrade, malfunction, manufacturer

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
	Predictor of risk of infection	Yes	OR for significant predictors: • Previous valvular surgery=1.525 • Cerebrovascular disease=1.172 • Chronic lung disease=1.215 • Renal failure-dialysis=1.342 • Replacement for device upgrade, malfunction, manufacturer advisory=1.354 • Adverse events=2.692 • Warfarin=1.155	P<0.050 (at least) for all variables reported	advisory is a risk factor for infection in patients with ICD/CRT-D implantation, but not a routine generator change due to normal battery depletion.
Kramer 2013[35]	Complication rates	Yes	• Replacement group (N=103,985)=0.9% • New implant group (N=359,993)=3.2%	Not reported	Patients undergoing ICD replacement had lower complication risks but higher death risk, compared to de novo implanted patients
	Median survival	Yes	• Replacement group (N=103,985)=2.0 years • New implant group (N=359,993)=2.5 years	Not reported	
	1-year mortality	Yes	• Replacement group (N=103,985)=9.9% • New implant group (N=359,993)=9.4%	P<0.0001	
	3-year mortality	Yes	• Replacement group (N=103,985)= 27.4% • New implant group (N=359,993)=23.5%	P<0.0001	

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
Palmisano 2013[36]	Complication rates per procedure-year	Yes	• Pacemaker implantation=1.70% • ICD implantation=3.47% • CRT device implantation=9.46% • Elective generator replacement=1.65% • Pacing system upgrade=6.06% • Overall= 2.82%	• P<0.0500 for paired comparisons between pacemaker, ICD, CRT-D implantation • P=0.9010 for comparison between pacemaker implantation and elective generator replacement • No other P values were reported	CRT implantation is the procedure with the highest risk of complications requiring surgical revision Elective generator replacements are not broken down by type of device (PM, ICD, CRT-D)

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size		Statistical test	Summary of main findings
	Complication-free survival, by type of initial procedure	Yes			P<0.0010	
Lovelock 2012[37]	1-year lead damage rates	Yes	• Replacement (N=72)=20.8% • Lead age matched control[(a)] (N=150)=2.5%		P<0.0010	Patients undergoing generator exchange had higher lead damage risk compared to subjects not requiring replacement
Uslan 2012[38]	Infection rates	No	Generator replacement (N=1,031)=1.4%	Generator replacement + lead revision (N=713)=1.1%	P=0.8300	The burden of infections associated with CIED replacements is limited; usage of preoperative antibiotics likely reduced the risk of procedural complications.

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size		Statistical test	Summary of main findings
Krahn 2011[39]	Overall complication rates	No	• Overall=4.3% • Major complication=2.6% • Minor complications=2.3%		-	Rates of complications associated with ICD/CRT-D replacement are substantial
	Complication rates associated with lead addition		Upgrade with addition of any lead=6.2% (CRT-Ds only)	Upgrade without addition of lead=5.9% (CRT-Ds only)	P=0.92	
Landolina 2011[40]	Infection rates	No	1% infection per year		-	Device-related events are particularly frequent in CRT-Ds (compared to single- or dual-chamber ICDs) and the risk increases with replacement procedures
	Predictors of risk of infection (HR): multivariate model	Yes	OR for significant predictors: • COPD=2.18 • Device replacement=2.04 • Valve disease=1.81		P=0.050 P=0.045 P=0.095	
Borleffs 2010[41]	Surgical re-intervention in first implanted ICD versus replacement ICD	Yes			P<0.0010	ICD replacement is associated with a doubled risk for pocket-related surgical reinterventions. The risk increases with every consecutive replacement

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
	Relationship between number of ICD replacements and the need for surgical reintervention			By comparing the ICs calculated for each rate per 100 ICD-years, statistically significant difference was found for the comparison between 2nd ICD and 1st ICD	
Nery 2010[42]	Infection rates Independent predictors of infection	Yes	• Overall=1.0% • Infection rates following replacement surgery/reoperation =2.1% • Infection rates following new device implantation=0.5%	Multivariate analysis (predictors) Device replacement (P=0.02); CRT/dual-chamber devices (P=0.048)	Pulse generator replacement surgery and dual- or triple-chamber device implantation are independent predictors of an increased risk of infection

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
Poole 2010[(c)43]	6-month complication rate	No	Major: • Replacement or upgrade with lead addition (Cohort 1) (N=713)=15.3%; CI 95% (12.70, 18.10) • Replacement or upgrade without lead addition (Cohort 2) (N=1,031)=4.0%; CI 95% (2.90, 5.40) Minor: • Replacement or upgrade with lead addition (Cohort 1) (N=713)=7.6%; CI 95% (5.70, 9.80) • Replacement or upgrade without lead addition (Cohort 2) (N=1,031)=7.4%; CI 95% (5.90, 9.10)	-	Pacemaker and implantable cardioverter-defibrillator generator replacements are associated with a notable complication risk, particularly those with lead additions
Costea 2008[44]	Complication rates related to replacement	No	Minor (total)=4.1% • Hematoma managed conservatively=2.7% • Minor discomfort due to protrusion =0.5% • Superficial skin infection=0.9% Major (total)=4.1% • Atrial lead damage=1.8% • Ventricular lead damage=0.5% • Hematoma requiring evacuation=0.5% • Pocket revision for protrusion=0.9% • Cerebrovascular accident=0.5%	-	Complications following deice replacements are not negligible, even in a hospital with a large experience

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
Gould 2008[45]	Complication rates	No	Major: 5.98% • Hematoma requiring reoperation=1.55% • System malfunction with reoperation=1.55% • Pocket infection requiring extraction=1.77% • Deaths=0.44% • Significant site pain with reoperation=0.67% Minor: 3.10% • Incisional infection medically management=1.77% • Significant site pain medically managed=0.44% • Exacerbation of medical condition=0.89%	-	Complications from advisory generator replacement are frequent. The risk of replacement is increased in patients with multiple previous pocket procedures
	Predictors of risk of complication	Yes	OR for significant predictors: Each additional procedure on pocket=2.53	P=0.022	
Kapa 2007[46]	Complication rates related to replacement	No	Total=1.24% • Infected devices=0.68% • Hematomas=0.41% • Incisional dehiscence=0.14%	-	Generator replacement is not a benign procedure and is associated to a certain risk for patients

Study name (Year)	Outcome	Comparison vs de novo implantations available	Effect size	Statistical test	Summary of main findings
Gould 2006[47]	Complication rates	No	Minor • Incisional infection, medically managed=1.7% • Significant site pain, medically managed=0.2% • Heart failure requiring admission=0.2% • Major psychological morbidity, medically managed=0.2% Major • Pocket infection requiring extraction=1.9% • Post-extraction deaths=0.4% • Hematoma requiring reoperation=2.3% • System malfunction requiring reoperation=1.5% • Significant site pain requiring reoperation=0.2%	-	Rates of complications associated with ICD replacement are substantial
Wild 2004[48]	Patient preference/ Patient satisfaction	No	• 90.1% of patients preferred a larger and longer-lasting device • Vs 9.9% of patients preferred a smaller device which requires more frequent surgeries	P<0.0001	The majority of patients prefer a larger device to reduce the number of potential replacement procedures

(a) Patients matched for Fidelis implant duration.

(b) Patients matched for Riata/Riata ST lead implant duration who did not undergo ICD replacement during follow-up.

(c) Patients undergoing generator replacement only.

(d) Patients undergoing generator replacement with planned lead addition or revision.

(e) Data are presented as total number of events occurred followed by the number of ICDs involved.

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

There have been a total of 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.[49]

The adverse event rates reported above are based on Medical Device Reports (MDRs) which capture all worldwide post-market adverse events for these devices. All MDRs are reported to the Food and Drug Administration (FDA) in the US and would be captured within the MAUDE database.[49]

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

The recent NICE technology appraisal[1] (TA314), published in June 2014, raised no safety concerns regarding CRT-D devices and recognised the ability of these devices to achieve important clinical benefits with an acceptable risk profile for the patients for which they are indicated. ENDURALIFE-powered CRT-D devices are considered safe when used in accordance with the Physician's Technical Manual.

See section 7.7.3 for further details on the safety profile for this technology.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.
Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Evidence synthesis through meta-analysis was not considered appropriate for this submission.

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Due to the predominantly observational and retrospective setting of these studies, a meta-analytic approach to synthesise evidence was not considered suitable. Meta-analyses and mixed treatment comparisons are generally conducted to summarise evidence from randomised clinical trials, each of them being powered to test specific outcome hypotheses.

Although the published observational studies included in this review showed good homogeneity in terms of patients' population and analysed clinical outcomes, factors such as variability of follow-up and inclusion of early vs modern generation devices would have limited the application of quantitative methods to summarise the evidence. Instead we have provided below a qualitative review of the evidence presented in sections 7.1 to 7.7.

Published studies

The evaluation of the clinical evidence included seven observational, predominantly retrospective studies which reported on battery survival of ENDURALIFE-powered CRT-D devices, previous generations of Boston Scientific devices and various competitor CRT-D devices. Table B14 below provides a summary of these results.

The seven studies included in the present review analysed a total of 8,801 patients, including 5,204 CRT-Ds. The total number of Boston Scientific CRT-Ds was 1,455 including 903 ENDURALIFE-powered CRT-Ds (62%). The clinical evidence showed that ENDURALIFE-powered devices exhibited increased longevity compared with that of other CRT-Ds included in the studies. Where univariate and multivariate analyses were included, device manufacturer was identified as a significant predictor of longevity.[16,17,20] Other important predictors of battery survival include battery capacity, LV impedance,[16] battery chemistry, high LV lead output, and unipolar LV lead.[17]

Improved longevity has been demonstrated to reduce the need for replacement procedures.[28] In order to assess the positive impact of reduced re-interventions on patient outcomes, we have carried out a review of the literature (see section 7.7.2). We identified 20 articles analysing outcomes associated to ICD and CRT-D replacement procedures, as well as the impact on patients' preferences and quality of life. This evidence shows that replacement interventions carry a certain level of risk of complications (e.g. infections, CV-related events, lead damage, etc.), [30,31,35,33,40,42,45-47] and that this risk is higher than the risk of complications in de-novo implanted patients.[34,36,39,42-44,47] Therefore, reducing the burden of replacements has positive implications for patients, as it decreases their exposure to potentially avoidable risks.

Unpublished studies

In addition to the above evidence pertaining to device survival and the associated burden of risks associated with replacement procedures, we identified five Product Performance Reports which reported survival probabilities for CRT-D device models with and without normal battery depletion.[22-26] A summary of results from these reports is presented above in Table B9. Since pulse generators are designed with a finite service life, their removal and return are a normal aspect of their use ("normal battery depletion").[27] The evidence here demonstrates that normal battery depletion is a more significant contributor to declining device survival than malfunctions, particularly as the devices age. This was a consistent result across all manufacturers.

Table B14 Summary of results of the studies listed in Table B3 and considered for the present review

Study name	Outcome	Longest follow-up available	BSC/ ENDURALIFE -powered	MDT	SJM	BTK	Sorin	Statistical significance	Manufacturer favoured
Alam 2016[15]	Risk reduction of battery depletion vs MDT devices	7 years	-85.0%	Reference	-54.0%	-	-	P<0.0010	BSC
	Rate of device replacement	Mean 3.4 years	16%	51%	53%	-	-	P<0.001	BSC
	ENDURALIFE-powered CRT-Ds cumulative survival	7 years	• Cognis=70% • Livian=0% • Renewal 3RF=0%	-	-	-	-	P<0.0010	BSC
Ellis 2016[16]	Proportion of batteries reaching ERI	Mean 3 years	0.3%	13.5%	3.8%	-	-	P<0.0010	BSC
	Odds ratio of battery capacity (Ah) as predictor of ERI	5 years (1,825 days)	-	9.73	-	-	-	P<0.0001	BSC/SJM
Landolina 2015[17]	Risk reduction of battery depletion vs MDT	5 years	-46.0%	Reference	-26.0%	-25.0%	-17.0%	BSC P<0.001, SJM P=0.089, BTK P=0.369, Sorin P=0.415; hazard ratio BSC vs. MDT=0.64 (multivariate analysis)	BSC
	Device survival (recent generation)	5 years	88.0%	52.0%	75.0%	-	-	P<0.01	BSC

Lau 2015[18]	Device survival to ERI	6 years	100.0%	0.0%	0.0%	-	-	P<0.0001 for BSC vs MDT; P=0.0018 for BSC vs SJM)	BSC
von Gunten 2015[19]	Battery survival (longevity) of CRT-Ds post-2006	6 years	97.6% (Highest performance)	46.3%	26.5% (lowest performance)	44.9%	-	P<0.0010	BSC
	Battery survival (longevity) for CRT-Ds, by model[(a)]	4 years	97.5% (Cognis)	• Concerto C 174=93.4 % • InSync III Marquis 7279=57. 1%	91.3% (Promote RF 3213)	95.0% (Lumax 540 HF-T)		Not reported	BSC (not confirmed if the differences are statistically significant)
Alam 2014[20]	Battery survival rates	4 years	94.0%	67.0%	92.0%	-	-	P<0.0010	BSC
	Rate of battery depletion	Mean 2.7 years	4.0%	25.0%	7.0%	-	-	P<0.0010	BSC
Williams 2014[21]	Battery depletion rates	4 years	1.9%	50.0%	10.0%	-	-	P<0.0010	BSC

(a) Findings shown in the Supplementary Material (Europace online).

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Key findings from all clinical evidence support the claimed clinical benefits and can be summarised as follows:

Findings from the clinical evidence	References
Longevity and battery survival	
There are significant differences in CRT-D battery longevity by manufacturer	Alam 2016,[15] Ellis 2016,[16] Landolina 2015,[17] Lau 2015,[18] von Gunten 2015,[19] Alam 2014,[20] Williams 2014[21]
In all 7 of the selected articles, BSC devices, and in particular ENDURALIFE-powered CRT-Ds (modern generation devices) showed longer battery survival, compared to other manufacturer devices analysed	Alam 2016,[15] Ellis 2016,[16] Landolina 2015,[17] Lau 2015,[18] von Gunten 2015,[19] Alam 2014,[20] Williams 2014[21]
Manufacturer was found among the strongest predictors of battery longevity in those studies analysing determinants of battery depletion	Ellis 2016,[16] Landolina 2015,[17] Alam 2014[20]
In addition to manufacturer, battery capacity, battery chemistry, and level of utilisation/drain are main predictors of battery longevity	Ellis 2016,[16] Landolina 2015,[17] Lau 2015,[18] Alam 2014,[20] Williams 2014[21]
Battery capacity: larger capacity CRT-Ds (i.e. 2Ah) are associated to increased longevity, compared to standard capacity devices (1.4 Ah, 1.0 Ah)	Ellis 2016[16]
Battery chemistry: LiMnO2 batteries ensure prolonged survival, compared to LiSVO batteries	Lau 2015[18]
Level of utilisation: low LV pacing impedance and increased LV pacing output are predictors of early battery depletion	Ellis 2016,[16] Landolina 2015,[17] Alam 2014,[20] Williams 2014[21]
Results from UK based population studies are consistent with non-UK studies in terms of comparative longevity across manufacturers	Lau 2015[18]
Overall device survival	
As the lifespan of a device increases, total device survival is increasingly driven by normal battery depletion rather than malfunctions	Biotronik PPR January 2016,[22] Boston Scientific PPR January 2016,[23] Medtronic PPR 2015 Second Edition,[24] Sorin PPR November 2015,[25] St Jude Medical PPR

	2016 First Edition[26]
Complications relating to replacement procedures	
Replacement procedures are associated with complications	Lewis 2016,[29] Nichols 2016,[30] Zeitler 2015,[32] Kramer 2013,[35] Prutkin 2014,[34] Palmisano 2013,[36] Lovelock 2012,[37] Uslan 2012,[38] Krahn 2011,[39] Landolina 2011,[40] Borleffs 2010,[41] Nery 2010,[42] Costea 2008,[44] Gould 2008,[45] Kapa 2007,[46] Gould 2006[47]
Typical complications of ICD/CRT-D replacements include: lead damage, infections, hematomas, pain, CV-adverse events, death	Nichols 2016,[30] Palmisano 2013 ,[36] Krahn 2011,[39] Poole 2010,[43] Costea 2008,[44] Gould 2008,[45] Gould 2006[47]
Risk of complications is typically higher in patients undergoing device replacement, compared to de novo implants and matched controls without replacement	Zeitler 2015,[31] Kramer 2013,[35] Lovelock 2014,[33] Prutkin 2014,[34] Palmisano 2013,[36] Lovelock 2011,[37] Landolina 2011,[40] Borleffs 2010,[41] Nery 2010,[42] Poole 2010,[43] Gould 2008[45]
Quality of life	
The current research did not identify quality of life studies evaluating the burden of ICD replacement	Not applicable
One study analysing patients' preferences shows that replacement is negatively perceived: patients prefer larger rather than smaller devices if this choice ensures increased longevity and reduced risk of replacement	Wild 2004[48]

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths

Analysed evidence shows a high level of consistency with the principal conclusions drawn above. Published evidence from the first systematic review (as described in sections 7.1-7.6) shows that ENDURALIFE-powered CRT-D devices had the longest battery survival among comparator CRT-Ds, consistently across all studies. In particular, the longevity benefit was clearly evident in all the comparisons versus Medtronic devices. These results were consistent across studies analysing UK (Lau 2014[18]) and non-UK patient populations.

A good level of consistency was found in the review of patients' outcomes associated to device replacement. The two main findings of this search (1. replacement is associated to a clinically relevant incidence of complications; 2.

complication rate is higher in replacement procedures, compared to de novo implantations) was consistent across most studies.

Limitations

In some of the analysed articles, only a proportion of patients (ranged from 39% to 100%) in the BSC groups were implanted ENDURALIFE-powered CRT-Ds (i.e. patients implanted with older generation devices were included in the cohort). It is likely that the mixed enrolment of ENDURALIFE-powered and CRT-Ds without ENDURALIFE Battery Technology could have biased the final longevity outcome and provided a more conservative picture of the performance of this technology.

A second limitation regards the level of comparability between different generations of CRT-D technologies. Some devices reported in the presented studies may not involve the most recent technologies on the market. However, we had to limit our analysis to published evidence and clinical evidence including long term follow up of the most recent technologies to the market is not available. We will try to address this in Section C with sensitivity analyses considering most recent device generations for competitor most recent devices.

Data from Product Performance Reports[22-26] presented in section 7.9.1 above is based on analysis of returned devices data which may not be representative of true malfunction or device survival due to bias relating to under-reporting. Furthermore, data may not be consistently captured across manufacturers depending on how proactive different companies are in requesting devices to be returned for analysis. There are also inherent differences in what “normal battery survival” is considered to be for different manufacturers and device models (as defined by the manufacturer in accordance with the published methodology for longevity estimates found in the device technical manuals) compared with an “premature battery depletion” malfunction. Thus, results are not considered to be comparable across manufacturers.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The evidence presented is consistent with the statement of the decision problem issued in the scope.[4]

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The evidence screened in this submission comes exclusively from observational studies and reflects clinical practice trends. Therefore, there are no issues of external validity/transferability to real clinical practice.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

There are no external validity factors limiting the usage of ENDURALIFE-powered CRT-Ds in specific patients' subgroups. Usage of ENDURALIFE-powered CRTD-s would be suitable in all patients requiring CRT-D implantation.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

Summary of economic evidence

- The evaluation of the economic evidence included:
  - 7 articles
  - A de novo economic analysis
- The evidence demonstrated that:
  - The evidence consistently showed a link between an increased device longevity and savings for the healthcare system [Section 8.2, 9.5, 9.8]
  - Results of the de novo cost model show that the 6-year therapy costs of one CRT-D patient would be £22,322 with ENDURALIFE-powered CRT-Ds; with Medtronic and St Jude Medical CRT-Ds 31% and 22% increase respectively [Section 9.5.2]
  - The analysis shows that for the NHS in England, the maximum savings would amount to £44 million over 6 years. This would significantly support the implementation of TA 314 and appropriate patient access to CRT-D therapy – at no increased cost for the NHS [Section 9.5]
  - ENDURALIFE-powered CRT-Ds remained a cost-saving option versus the comparators in all sensitivity analyses [Section 9.5.6, 9.5.7, 9.5.8, 9.5.9]

8 Existing economic evaluations

8.1 Identification of studies

A systematic literature review was conducted to identify relevant studies focused on the economic impact of extending longevity of CRT-D devices.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10.6

A systematic approach to identify economic evaluations was followed, analysing the following sources:

(iv) Pubmed;

(v) Cochrane;

(vi) ClinicalTrials.gov

Additionally, hand-searching of internal company documentation was performed in order to collect studies not indexed. Please refer to the PRISMA diagram in Figure C1 for the algorithm of search.

This review is based on a search conducted on May 27th 2016. The studies identified were independently assessed by a reviewer in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by this second reviewer. See section 10.6 for full details of the search strategy used.

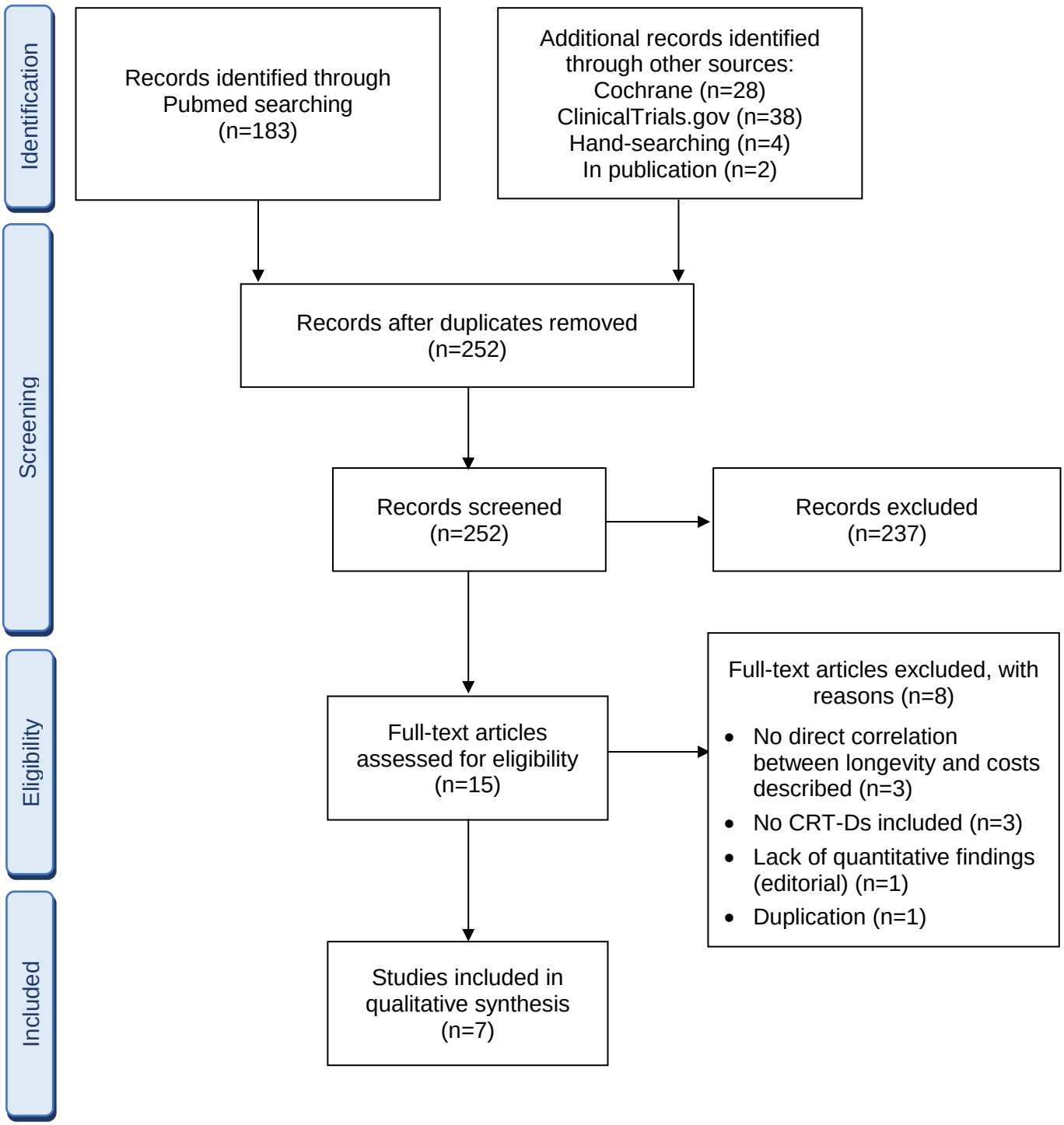
8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients implanted with CRT-Ds
Interventions	CRT-Ds
Outcomes	Costs, budget impact, cost-effectiveness relating to device longevity
Study design	All studies reporting CRT-D economic outcomes related to longevity were included
Language restrictions	English language only
Search dates	No restrictions
Exclusion criteria	
Population	Patients implanted exclusively with ICDs (i.e. ICD-VR, ICD-DR) or pacemakers, not CRT-Ds
Interventions	Studies where patients with implanted CRT-Ds were not analysed
Outcomes	-
Study design	Non-comparative studies/editorials/reviews
Language restrictions	English language only
Other restrictions	No full text or abstract available
Search dates	-

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure C1 PRISMA flow diagram for economic search



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope.

The economic literature review evaluated 7 published studies, reporting on economic implications of battery survival of CRT-D devices.

Table C2 Summary list of all evaluations involving costs - [redacted]

Study name (year)	[redacted]50
Study design	- [redacted] Error! Bookmark not defined. [redacted]
Patient population	• [redacted]
Costs	• [redacted]
Patient outcomes	• [redacted]
Results	• [redacted]

	[redacted]

Table C3 Summary list of all evaluations involving costs - [redacted]

Study name (year)	[redacted]
Study design	[redacted]
Patient population	[redacted]
Costs	[redacted]
Patient outcomes	[redacted]
Results	[redacted]

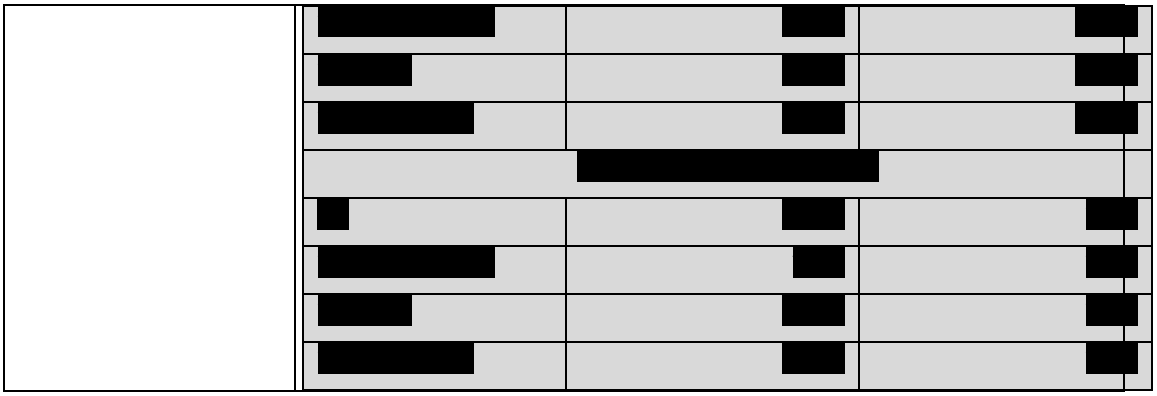


Table C4 Summary list of all evaluations involving costs - Chung 2015

<table>
<tr><td>Study name (year)</td><td>Chung 2015[52]</td></tr>
<tr><td>Study design</td><td>• Objective: to measure cost savings associated with incremental months/years of battery life
• Type of study: economic model based on 7 prospective observational studies and statistical modelling of device survival
• Time horizon: not reported (device longevity range: 5.5-8.5 years)
• Perspective: Healthcare system (Medicare)
• Comparators: Three patient subgroups: NYHA class III/IV; NYHA class II; AV block. Longevity evaluated at 6-monthly increments from 5.5 years to 8.5 years</td></tr>
<tr><td>Patient population</td><td>• Patients implanted with CRT-Ds
• Population enrolled in 7 prospective studies (InSync III Marquis, MIRACLE, MIRACLE ICD, PROSPECT, Adaptive CRT, REVERSE, BLOCK-HF)</td></tr>
<tr><td>Costs</td><td>Medicare costs (procedures + devices). Cost of complications related to replacements are not included</td></tr>
<tr><td>Patient outcomes</td><td>Mean devices per patient, by device longevity and indicated patient group
<table>
<tr><th>Mean CDT-D generator longevity</th><th>NYHA class III/IV</th><th>NYHA class II</th><th>AV block class</th></tr>
<tr><td>5.5 years</td><td>1.99</td><td>3.12</td><td>2.41</td></tr>
<tr><td>6.0 years</td><td>1.87</td><td>2.90</td><td>2.24</td></tr>
<tr><td>6.5 years</td><td>1.79</td><td>2.73</td><td>2.13</td></tr>
<tr><td>7.0 years</td><td>1.72</td><td>2.58</td><td>2.04</td></tr>
<tr><td>7.5 years</td><td>1.66</td><td>2.46</td><td>1.94</td></tr>
<tr><td>8.0 years</td><td>1.60</td><td>2.33</td><td>1.86</td></tr>
<tr><td>8.5 years</td><td>1.54</td><td>2.22</td><td>1.78</td></tr>
</table></td></tr>
</table>

Results

Increased CRT-D battery life resulted in substantial reductions of device-related costs across all indicated patient groups, with economic benefits maximised among NYHA Class II patients

Total device-related costs, per patient

Mean CDT-D generator longevity	NYHA class III/IV ($)	NYHA class II ($)	AV block class ($)
5.5 years	70,754	111,072	85,626
6.0 years	66,544	103,314	79,790
6.5 years	63,805	97,050	75,946
7.0 years	61,349	91,783	72,458
7.5 years	59,070	87,370	69,149
8.0 years	56,962	82,993	66,302
8.5 years	54,853	79,007	63,454

Saving per incremental longevity, per patient

Mean CDT-D generator longevity	NYHA class III/IV ($)	NYHA class II ($)	AV block class ($)
5.5 years			
6.0 years	4,210	7,758	5,837
6.5 years	2,739	6,264	3,844
7.0 years	2,456	5,267	3,488
7.5 years	2,279	4,413	3,310
8.0 years	2,108	4,377	2,847
8.5 years	2,108	3,986	2,847

Savings associated to 6 additional months of device longevity:

- $2,650 for Class III/IV patients
- $5,344 for Class II patients
- $3,695 for AV Block patients

Table C5 Summary list of all evaluations involving costs - Priest 2015

<table>
<tr><td>Study name (year)</td><td>Priest 2015[53]</td></tr>
<tr><td>Study design</td><td>

Objective: to assess the long-term economic benefits of improved ICD and CRT-D battery longevity in devices with a 1.7-2.0 Amp hour (Ah) capacity and Li/MnO2 chemistry
Type of study: economic model based on a previously published economic model Boriani 2013[55]
Time horizon: 15 years
Perspective: Healthcare system
Comparators:

Devices with industry-standard battery longevity
Devices with extended battery longevity

</td></tr>
<tr><td>Patient population</td><td>Patients implanted with CRT-Ds</td></tr>
<tr><td>Costs</td><td>Device, procedure costs:

Initial device costs were informed by the average selling prices for each constituent component (2014 Price Waterhouse Coopers analysis)
Hospital costs were informed by 2010/2011 Australian DRG
Costs were discounted at 5% per annum

</td></tr>
<tr><td>Patient outcomes[(a)]</td><td>Average Device Longevity and number of implants
<table>
<tr><th>Device</th><th>Industry-Standard Devices</th><th>Extended-Longevity Device[(b)]</th></tr>
<tr><td>CRT-D</td><td>5.8 years</td><td>9.1 years</td></tr>
<tr><td>N. De Novo Patients</td><td>19,740</td><td>25,127</td></tr>
<tr><td>N. Replacements</td><td>12,234</td><td>5,382</td></tr>
</table>
</td></tr>
<tr><td>Results[(a)]</td><td>Increasing use of longer-lasting devices resulted in substantial cost-savings and improved resource use over 15 years
Total cost per patient
<table>
<tr><th>CRT-D</th><th>Industry-Standard Devices</th><th>Extended-Longevity Devices**</th></tr>
<tr><td>Cost per patient in $AU</td><td>61,954</td><td>48,672</td></tr>
</table>

If all patients implanted used devices with extended-longevity, this would result in cost savings of more than AU$900 million over 15 years
Device replacement can also be associated with complications. This analysis does not consider this typology of cost so results may underestimate the savings associated with improved device

</td></tr>
</table>

	longevity

(a) Results for CRT-Ds only were extrapolated. Also results for ICDs were available in the article.

(b) Devices with 1.7-2.0 amp hour (Ah) capacity and Li/MnO2 chemistry

Table C6 Summary list of all evaluations involving costs - Duxbury 2014

Study name (year)	Duxbury 2014[54]
Study design	• Objective: to evaluate the impact on the NHS of using extended longevity devices • Type of study: cumulative budget impact analysis based on a previously published economic model Boriani 2013[55] • Time horizon: 10 years • Perspective: UK NHS • Comparators: - Devices with extended battery longevity (13.1 years for ICD VR, 11.5 years for ICD DR, and 9.6 years for CRT-D) - Devices with industry-standard battery longevity (7.1 years for ICD VR and DR, 5.8 years for CRT-D)
Patient population	Total number of patients implanted with ICDs/CRT-Ds in the English NHS in 2013
Costs	Device, procedure, hospitalisation costs
Results	• Implantation of ICD/CRT-D devices with extended longevity could result in potential savings of up to £144 million over 10 years • Implantation of ICD/CRT-D devices with extended longevity could reduce replacement procedures by 8,500 and therefore increase access to services for new patients • No explicit results for CRT-Ds reported

Table C7 Summary list of all evaluations involving costs - Boriani 2013

<table>
<tr><td>Study name (year)</td><td>Boriani 2013[55]</td></tr>
<tr><td>Study design</td><td>• Objective: to determine the cost impact of extending device longevity in four patient populations requiring a single-chamber ICD or CRT-D (only two of the four patient populations received CRT-D therapy and are reported in the summary below)
• Type of study: economic model looking at varying device longevities in a ‘real-world’ clinical setting
• Time horizon: 15 years
• Perspective: hospital</td></tr>
<tr><td>Patient population[(a)]</td><td>Patients implanted with CRT-Ds
- Population C: Patients with impaired LV function, mild heart failure and wide QRS (N=not reported)
- Population D: Patients with impaired LV function, moderate heart failure and wide QRS (N=not reported)</td></tr>
<tr><td>Costs</td><td>Device, procedure, complications, follow-up costs were derived from published sources and expert consensus</td></tr>
<tr><td>Results</td><td>With regard to all the populations considered, implantation of devices with extended longevity was cost-saving, compared with implantation of devices with shorter survival

Per-patient costs over 15 years - Population C
<table>
<tr><th>Cost item</th><th>4-year longevity (€)</th><th>7-year longevity (€)</th><th>Saving 7 vs. 4-year longevity (€)</th></tr>
<tr><td>Total</td><td>43,762.66</td><td>30,132.29</td><td>13,630.38</td></tr>
<tr><td>1st implant</td><td>21,020.35</td><td>21,020.35</td><td>0.00</td></tr>
<tr><td>1st replacement</td><td>10,724.39</td><td>8,423.34</td><td>2,301.05</td></tr>
<tr><td>2nd replacement</td><td>7,777.72</td><td>688,6</td><td>7,089.12</td></tr>
<tr><td>3rd replacement</td><td>4,240.16</td><td>-</td><td>4,240.16</td></tr>
</table>
Relative cost saving: 31%

Per-patient costs over 15 years - Population D
<table>
<tr><th>Cost item</th><th>4-year longevity (€)</th><th>7-year longevity (€)</th><th>Saving 7 vs. 4-year longevity (€)</th></tr>
<tr><td>Total</td><td>38,469.56</td><td>27,501.28</td><td>10,968.26</td></tr>
<tr><td>1st implant</td><td>20,914.71</td><td>20,914.71</td><td>0.00</td></tr>
<tr><td>1st replacement</td><td>9,547.32</td><td>6,212.05</td><td>3,335.27</td></tr>
<tr><td>2nd replacement</td><td>5,491.73</td><td>374.52</td><td>5,117.21</td></tr>
<tr><td>3rd replacement</td><td>2,515.78</td><td>-</td><td>2,515.78</td></tr>
</table>
Relative cost saving: 29%</td></tr>
</table>

(a) Two other groups (populations A and B) were available in the article but referred to ICDs only.

Table C8 Summary list of all evaluations involving costs - Biffi 2011

<table>
<tr><td>Study name (year)</td><td>Biffi 2011[56]</td></tr>
<tr><td>Study design</td><td>

Objective: to calculate the daily cost of implantable cardioverter-defibrillators based on their actual longevity
Type of study: economic analysis from a prospective, single-centre observational study[57]
Time horizon: median follow-up of the study = 7.7 years
Perspective: hospital
Comparators: for all the manufacturers, results for single chamber ICDs (N=63), dual chamber ICDs (N=50) and CRT-Ds (N=10) were reported:

Medtronic (n=23)
Guidant (now Boston Scientific) (n=43)
St Jude Medical (n=57)

</td></tr>
<tr><td>Patient population</td><td>

Patients implanted with ICDs/CRT-Ds
Population derived from Biffi 2008

</td></tr>
<tr><td>Costs</td><td>Device, procedure and hospitalisation costs</td></tr>
<tr><td>Patient outcomes</td><td>

Mortality rate during the study was 7.6%
Medtronic devices exhibited higher longevity than Guidant and St Jude Medical devices

</td></tr>
<tr><td>Results</td><td>

Overall (for all groups; single chamber ICDs, dual chamber ICDs and CRT-Ds devices with extended longevity resulted in cost-savings
The difference in cost between manufacturers was not statistically significant in the CRT-D group (likely because of the small sample size)

Cost per service life up to replacement, in the CRT-D group (N=10)
<table>
<tr><th>Group</th><th>Daily cost (€)</th><th>Up-front costs (€)</th></tr>
<tr><td>Medtronic</td><td>8.5</td><td>20,932</td></tr>
<tr><td>Guidant</td><td>15.4</td><td>20,962</td></tr>
<tr><td>St Jude Medical</td><td>14.6</td><td>19,775</td></tr>
<tr><td>P (Kruskal-Wallis test)</td><td>0.100</td><td>0.080</td></tr>
</table>
</td></tr>
</table>

8.2.2 Provide a complete quality assessment for each health economic study identified.

Table C9 Quality assessment of health economic studies

Study question	[redacted]	[redacted]	Chung 2015[52]	Priest 2015[53]	Duxbury 2014[54]	Boriani 2013[55]	Biffi 2011[56]
1. Was the research question stated?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	[redacted]	[redacted]	No	No	No	No	No
8. Was/were the source(s) of effectiveness estimates used stated?	[redacted]	[redacted]	No	Yes	N/R	N/R	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	[redacted]	[redacted]	No	No	N/R	N/R	Yes

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
13. Were the details of the subjects from whom valuations were obtained given?	[redacted]	[redacted]	No	No	No	No	Yes
14. Were productivity changes (if included) reported separately?	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A
16. Were quantities of resources reported separately from their unit cost?	[redacted]	[redacted]	No	Yes	No	Yes	No
17. Were the methods for the estimation of quantities and unit costs described?	[redacted]	[redacted]	No	Yes	No	Yes	No
18. Were currency and price data recorded?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	[redacted]	[redacted]	No	Yes	No	Yes	No
20. Were details of any model used given?	[redacted]	[redacted]	No	No	No	Yes	N/A

21. Was there a justification for the choice of model used and the key parameters on which it was based?	[redacted]	[redacted]	No No	No	No N/A	No Yes	N/A
22. Was the time horizon of cost and benefits stated?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
23. Was the discount rate stated?	[redacted]	[redacted]	No	Yes	No	Yes	No
24. Was the choice of rate justified?	[redacted]	[redacted]	No	No	No	Yes	No
25. Was an explanation given if cost or benefits were not discounted?	[redacted]	[redacted]	No	N/A	No	N/A	No
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	[redacted]	[redacted]	No	No	No	No	Yes
27. Was the approach to sensitivity analysis described?	[redacted]	[redacted]	N/A	N/A	N/A	Yes	N/A
28. Was the choice of variables for sensitivity analysis justified?	[redacted]	[redacted]	N/A	N/A	N/A	No	N/A
29. Were the ranges over which the parameters were varied stated?	[redacted]	[redacted]	N/A	N/A	N/A	Yes	N/A
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
31. Was an incremental analysis reported?	[redacted]	[redacted]	Yes	No	No	Yes	No
32. Were major outcomes presented in a disaggregated as well as aggregated form?	[redacted]	[redacted]	No	Yes	No	No	No

33. Was the answer to the study question given?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	[redacted]	[redacted]	Yes	Yes	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	[redacted]	[redacted]	No	No	No	Yes	Yes
36. Were generalisability issues addressed?	[redacted]	[redacted]	No	No	No	Yes	Yes

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

A de novo cost analysis was undertaken to estimate the impact on cost and outcomes of ENDURALIFE-powered CRT-D devices compared to other CRT-D devices not incorporating ENDURALIFE Battery Technology from a UK NHS perspective, as outlined in the scope.[58] While other economic evaluations have recently assessed the economic impact of increased longevity of one manufacturer versus another, only one (Duxbury 2014[54]) was based on a UK NHS perspective. This study reported total cost savings for both ICDs and CRT-Ds and did not report the cost impact for CRT-D devices separately. Furthermore, this study was published as an abstract only, with limited information as to the methodology of the analysis. For these reasons, it was felt a de novo cost model was necessary to fully assess the cost impact of the technology versus comparators for the purposes of this submission.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

In line with the scope issued by NICE,[58] the cost analysis incudes heart failure patients indicated for CRT-D devices as per NICE Technology Appraisal 314[59].

Figure **C2** in section 9.1.4 summarises the specific patient subgroups indicated for such a device.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

The comparators used in cost analysis are CRT-D devices not incorporating ENDURALIFE Battery Technology and are in line with the scope.[58] The comparators in the cost analysis do not include all manufactures available on UK market due to lack of data in the published literature (see Section 9.2.1).

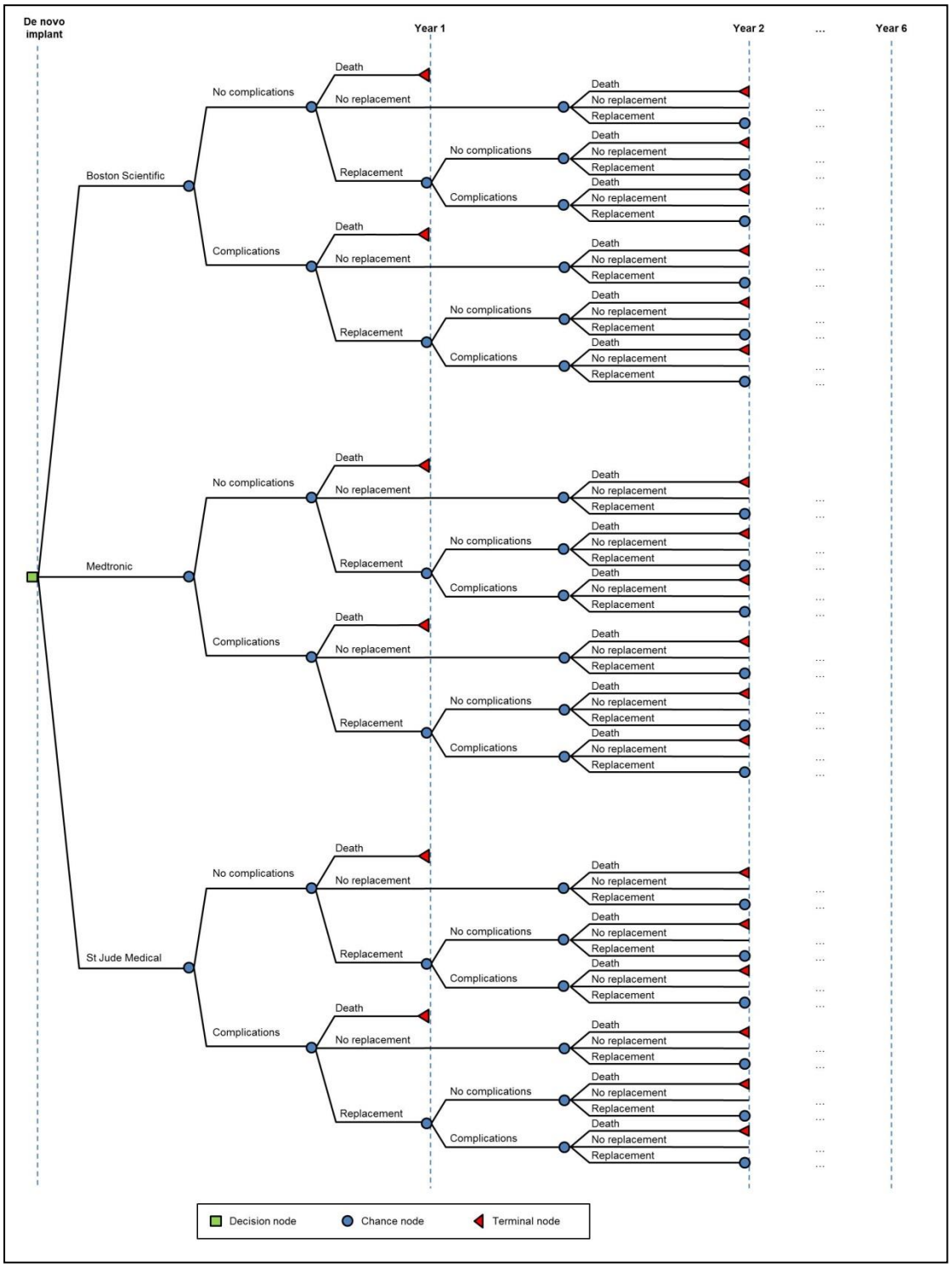
Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

Figure **C2** below illustrates the model structure used in the de novo cost analysis in the form of a decision tree for patients undergoing an initial CRT-D implantation. This model structure is the same as that used in the [redacted] economic analysis.
The single decision node in the model represents the choice to use a particular manufacturer of CRT-D device – i.e., whether to use an ENDURALIFE-powered CRT-D device or a comparator CRT-D device. The decision to include only 3 possible options here (i.e., Boston Scientific's ENDURALIFE-powered CRT-D devices, Medtronic CRT-D devices or St Jude Medical CRT-D devices) is justified in section 9.2.1 below.

The decision tree representation of the model also depicts two types of chance node. The first reflects the chance of a post-operative complication requiring treatment (and therefore incurring costs) arising as a result of any intervention that a patient may undergo (initial implant or replacement). The second type of chance node reflects the three possible outcomes for a patient at the end of each year. At the end of each year, there is a risk of mortality (all-cause; leading to a terminal node) or for those surviving patients, a chance that the battery of their CRT-D device will deplete and require a replacement device to be implanted or a chance that the patient will continue to progress to the following cycle with no further action being taken.

Figure C2 Decision tree illustrating model structure



The decision tree illustrated in

Figure C2 C2 shows the possible pathways for the first two full cycles only. The same approach has been applied in the cost model for the remaining four cycles, with a model end-point after six full cycles, i.e., at six years after the initial CRT-D implantation of the patient.

The above model structure has been used in the de novo cost analysis to evaluate the cost and resource implications of the choice of CRT-D device for:

- A single patient over six years following the initial implantation of a CRT-D device
- The broader perspective for the NHS in England over a six-year period. The NHS analysis reports results for the overall CRT-D population (N = 3,031 in 2014/15[60]). It assumes that 3,031 patients are implanted every year. This would represent a more realistic impact analysis for the NHS rather than following the same initial cohort for 6 years.

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The de novo cost analysis focuses only on those patients indicated for and implanted with a CRT-D device, as described in section 9.1.2 above. As such, it reflects only the treatment and care of these patients and excludes any interventions or care the patients may receive before or after this step of the patient pathway.

The chosen model structure reflects a simplified version of current clinical practice, notably:

- Patients are implanted with a CRT-D device at year 0
- Each year, there is a risk of mortality (all-cause, including as a result of heart failure progression)
- For those patients alive at the end of each year, there is a risk that the device will reach the end of its battery life and require a replacement device to be implanted

- Patients are at risk of post-operative complications after each intervention (initial implant or replacement procedures)

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table C10 De novo cost model assumptions

Assumption	Justification
All patients entering the model are indicated for and undergo implantation of a CRT-D device as per TA314[61]	This is in line with the population identified in the scope.[58]
Patient survival is considered to be the same regardless of device choice	There is no data to suggest otherwise.
Device costs are based on average selling prices rather than list prices and are the same for the technology and all comparators	List prices were not used as they are seldom used when selling to hospitals and do not adequately reflect the actual cost to the NHS of these devices. Costs are instead based on the average selling prices for the UK NHS across all manufacturers used in the economic modelling for NICE's Technology Appraisal 314[59]. Given the significant variation in device cost across the NHS for all manufacturers as a result of purchasing agreements, it was felt costs based on this source better represented the true financial impact of these devices on the NHS. Sensitivity analyses will test this assumption
Initial implant and replacement procedure costs are based on NHS tariffs and are included in the model in addition to the device cost	NHS tariffs are an appropriate cost base as they reflect the actual cost to the NHS of performing these procedures (i.e., healthcare system perspective rather than an individual provider perspective). Under the current 2016/17 National Tariff Payment System,[66] the HRG tariffs are paid in addition to the cost of the device under exclusion for "ICD with CRT (Cardiac Resynchronisation Therapy) capability" on the High Cost Devices list
Initial implant and replacement procedures are assumed to be reimbursed as elective/day case procedures, excluding Market Forces Factor variations	This is a conservative assumption and is in line with assumptions used in the economic modelling for NICE's Technology Appraisal 314[59]
Device malfunctions are not considered to be a significant driver of device failure when compared against battery depletion and therefore are excluded from the cost analysis	Normal battery depletion is a more significant contributor to declining device survival than malfunctions, therefore the model focused on device survival due to battery depletion and excluded malfunctions (see section 7.9)
Complication rates are assumed to be the same for initial implant	This is a conservative assumption and is in line with assumptions used in the economic modelling for NICE's

and replacement procedures in the base case	Technology Appraisal 314[59]
There is a maximum of three replacements that could be performed over the model time horizon	Based on [redacted] device survival for all manufacturers was [redacted], therefore replacement procedures would be expected to happen in years 2, 4 and 6 (in the worst case scenario)
Routine follow-up appointments are expected to happen semi-annually	In line with nationally accepted intervals for follow-ups "max. 6 monthly" (post-implantation), as outlined in NHS England service specifications for ICD and CRT procedures (NHS England 2013[62])
An additional follow-up is conducted after any CRT-D related procedure (initial implant or replacement) NOTE: this excludes procedures relating to complications	In line with nationally accepted intervals for follow-ups "within 2 months" of implantation, as outlined in NHS England service specifications for ICD and CRT procedures (NHS England 2013[62])
Urgent follow-ups are excluded from the model	There is no relevant data on which to base this parameter
Warranties deemed eligible and taken up by the NHS are assumed to be claimed at the mid-point of the year in which they expire	A standard warranty will apply pro-ration on a daily basis. However, given the annual data points utilised in the cost analysis it is not possible to apply the warranty credits in this way. In order to be conservative we have assumed that any devices which do not survive any given year will have expired at the mid-point of that year

9.1.7 Define what the model's health states are intended to capture.

Health states are not used in the de novo cost analysis.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C11 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	6 years	Based on the time horizon of the [redacted][51] data on which the model's device survival is based and in line with the scope by being "sufficiently long to reflect any differences in costs and consequences between the technologies being compared"	[redacted][51]; NICE 2016[4]
Discount rate	3.5% (applied to all costs beyond the first year)	In line with NICE reference case	NICE 2011[67]
Perspective	NHS	In line with NICE reference case and scope	NICE 2011[67]; NICE 201[64]
Cycle length	1 year	Based on the frequency of data points reported in [redacted][51] for device survival and Yao 2007[63] for patient survival	[redacted][51]; Yao 2007[63]

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Data on CRT-D battery survival used as an input to the cost analysis was obtained from a previously published cohort reported in [redacted][51]. The study design and patient characteristics for this cohort have been reported earlier in this submission as part of the cost evidence presented. This study was selected for the base case as it is a contemporary study and the only one to contain exclusively ENDURALIFE-powered CRT-D devices in the Boston Scientific cohort. The comparison of device survival among recent-generation CRT-D devices from different manufacturers was performed only for subgroups with at least 100 devices in analysis. As such, battery survival data for devices manufactured by Boston Scientific, Medtronic and St Jude Medical was taken from this study and incorporated into the cost analysis (see Table C12).

The other studies reported in Section B were not considered as relevant as the Italian cohort in [redacted][51]. However, it is worth noting that the 5-year probability of device survival reported in Ellis 2016[16] is in line with the [redacted] analysis and corroborates our main clinical assumptions.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Not applicable.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Not applicable.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events in the form of complications arising from replacement CRT-D procedures, as identified in section 7.7, have been incorporated into the cost analysis. In order to tailor the cost analysis to reflect real-world clinical practice as closely as possible, the model was structured to include both replacement and initial implant complication rates. While we have previously identified 20 relevant studies (see section 7.7.1), few were high quality systematic reviews or meta-analyses and those that were did not report a comparison of complication rates for both initial implant and replacement procedures. Therefore, we concluded that the base-case could not be based on any of the 20 studies. Instead we have incorporated all major complications used in the economic evaluation performed for NICE's Technology Appraisal 314[59]:

- Infection
- Complication requiring re-intervention
- Device-pocket problem requiring revision

This evaluation was deemed to be a high quality predicate on which to model post-operative complications for the base case. Using this approach, we have assumed

initial implant and replacement complications to occur at the same frequency. This is a conservative assumption as replacement procedures have shown a higher rate of complications (see section 7.8.2).

Complication rates from the systematic review from Lewis and colleagues[29] (included in the clinical evidence section) were used as part of the sensitivity analysis (see section 9.4).

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Not applicable.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission.

The three main clinical variables used in the de novo cost analysis are summarised in

Table C12. They include:

- Cumulative probability of device survival
- Cumulative probability of patient survival
- Incidence of complications

In the absence of UK-specific data on CRT-D patient survival, cumulative probability of patient survival was taken from Yao 2007[63]. This source was used as the base case as it is based on the CARE-HF landmark RCT and provides information on long-term patient survival in order to populate the economic model.

The justification for the source of data for cumulative probability of device survival data and incidence of complications are described elsewhere in sections 9.2.1 and 9.2.4 respectively.

Table C12 Summary of clinical variables applied in the cost model

Variable	Enduralife-powered CRT-Ds (Boston Scientific)	Medtronic CRT-Ds	St Jude Medical CRT-Ds
Cumulative probability of patient survival[63]			
Year 0	100%		
Year 1	95%		
Year 2	90%		
Year 3	85%		
Year 4	81%		
Year 5	77%		
Year 6	72%		
Cumulative probability of device survival Error! Bookmark not defined.			
[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]
Incidence of complications (initial implant and replacement procedures)[64]			
Infection	2.4%		
Complication requiring re-intervention[(a)]	8.5%		
Device-pocket problem requiring revision	0.5%		

Frequency of follow-up appointments per year[62]	
Post-procedure follow-ups	1
Ongoing routine follow-ups	2

(a) Includes lead dislodgement and haematomas requiring intervention

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The procedural costs for initial and replacement CRT-D implants are currently reimbursed under HRGs EA56Z and EA12Z respectively. These HRGs have been identified by applying the HRG4 2016/17 Local Payment Grouper[65] to the OPCS codes described in section 9.3.2 below. The reimbursement for these HRGs is shown in Table C13.

Table C13 2016/17 Admitted patient care tariffs for CRT-D procedures

Procedure	HRG	Description	Combined day case / ordinary elective spell tariff	Non-elective spell tariff
Initial CRT-D implant procedure	EA56Z	Implantation of Cardiac Resynchronization Therapy Defibrillator (CRT-D)	£6,201	£13,962
Replacement CRT-D procedure	EA12Z	Implantation of Cardioverter; Defibrillator only	£4,700	£6,260

In addition to the tariff, the NHS also reimburses providers for the cost of the device under exclusion for “ICD with CRT (Cardiac Resynchronisation Therapy) capability” on the High Cost Devices list[66]. At the time of submission, national procurement for these devices has yet to be implemented in the NHS and as such, reimbursement is assumed to reflect the actual cost to the provider of purchasing these devices as per local pricing rule 7[66] – i.e., total reimbursement to the NHS will on average be equal

to the above tariff plus the average selling price of the device used for the initial implant or replacement procedure.

Reference Costs are available for the financial year 2014/15. However, for the purposes of the de novo cost analysis, we have taken the perspective of the NHS as a whole rather than an individual provider perspective. As such, we have used the national tariffs presented in Table C13 plus the average selling price of the CRT-D system/implantable pulse generator as shown in section 9.3.7 below to represent the total financial burden to the NHS of performing these procedures.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

Table C14 below outlines the relevant OPCS codes relating to initial and replacement CRT-D implant procedures.

Table C14 OPCS codes relating to CRT-D procedures

Procedure	OPCS code	Description
Initial CRT-D implant procedure	K596	Implantation of cardioverter defibrillator using three electrode leads
Replacement CRT-D procedure	K594	Renewal of cardioverter defibrillator[(a)]

(a) Note: includes renewal of ICDs and CRT-Ds. Currently no OPCS code specific to CRT-D replacement exists.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Targeted searches were performed to identify relevant point estimates for cost and resource input parameters to identify inputs relevant for the NHS rather than conducting a systematic search.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

Not applicable.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

Not applicable (see section 9.3.6 below).

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

List prices were not used in the de novo cost model as they are seldom used when selling to hospitals and do not adequately reflect the actual cost to the NHS of these devices.

The model uses a mean cost of £12,404 for a complete CRT-D system and £11,858 for a replacement implantable pulse generator only (excluding leads) for both ENDURALIFE-powered CRT-Ds and comparator CRT-Ds. These costs are based on the average selling prices for the UK NHS across all manufacturers used in the economic modelling for NICE's Technology Appraisal 314[59], and have been inflated[67] for our analysis using the 2015 Bank of England inflation rate of 0.9%[68].

Given the significant variation in device cost across the NHS for all manufacturers as a result of purchasing agreements, it was felt costs based on this source better represented the true financial impact of these devices on the NHS.

Despite the superiority of the ENDURALIFE-powered CRT-Ds, there is no price premium attached to the technology and we have assumed a similar price across all manufacturers.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. Tables should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Device

Table C15 shows the device costs used in the cost analysis. These costs are assumed to be equivalent for ENDURALIFE-powered CRT-Ds and comparator CRT-Ds as described in section 9.3.6 above.

Table C15 Device costs per procedure used in the cost analysis

Items	Value	Source
CRT-D system[(a)]	£12,404	NICE TA314 economic modelling [59]; 2014 costs reported (£12,293) were inflated to 1/1/2016
CRT-D replacement device[(b)]	£11,858	NICE TA314 economic modelling [59]; 2014 costs reported (£11,752) were inflated to 1/1/2016

(a) CRT-D system cost includes price of implantable pulse generator and leads/accessories for initial implant.

(b) CRT-D replacement device cost includes cost of implantable pulse generator only.

Procedure

Table C16 shows the procedure costs and associated resource implications used in the base case of the cost analysis. Procedure costs were based on the 2016/17 National Tariff Payment System[66] to reflect the cost to the NHS of performing these procedures and are in addition to the device costs described above, as outlined in section 9.3.1 above. A conservative approach was taken using elective tariffs (as only 10% of procedures were recorded as emergency admissions in 2014/15[60]) and excluding Market Forces Factor variations.

Table C16 Procedure costs used in the cost analysis

Items	Value	Source
Initial CRT-D implantation	£6,201	Combined day case/ordinary elective spell tariff for HRG EA56Z; NHS National Tariff Payment System 2016/17[66]
CRT-D replacement	£4,700	Combined day case/ordinary elective spell tariff for HRG EA12Z; NHS National Tariff Payment System 2016/17[66]

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table below. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Removed; not relevant.

Adverse-event costs

9.3.9 Complete table with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table C17 and Table C18 outline the cost and resource implications used in the cost analysis for adverse events.

Table C17 List of adverse events and summary of costs included in the cost model

Adverse events	Value	Reference
Infection	£21,774	NICE TA314 economic modelling[59]; 2014 costs reported (£21,580) were inflated to 01/01/2016
Complication requiring re-intervention[(a)]	£6,152	NICE TA314 economic modelling[59]; 2014 costs reported (£6,097) were inflated to 01/01/2016
Device-pocket problem requiring revision	£18,010	NICE TA314 economic modelling[59]; 2014 costs reported (£17,849) were inflated to 01/01/2016

(a) Includes lead dislodgement and haematomas requiring intervention

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

10 In addition to the above costs,

Table **C**18 lists additional miscellaneous costs associated with follow-up appointments which are included within the cost analysis. Routine follow-up appointments are expected to happen semi-annually, with an additional follow-up conducted after initial implantation or replacement procedures, as described in Table C10 above. These appointments are not considered to add any additional resources in terms of invasive procedures as they are considered outpatient appointments.

Table C18 Miscellaneous costs used in de novo cost analysis

Item	Value	Source
Follow-up appointment	£96	Outpatient Attendance for Treatment Function 320: Cardiology (WF01A – Follow-up Attendance – Single Professional); 2016/17 National Tariff Payment System[66]

10.1.1 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No, implications for all relevant resources have been quantified.

10.2 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

10.2.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

Yes, the uncertainty around structural assumptions has been investigated through one-way sensitivity analyses.

10.2.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

In our model, a range of univariate deterministic sensitivity analyses were conducted to explore the sensitivity of the results (cost per patient) to the clinical and cost input parameters. It was concluded that in this case a univariate sensitivity analysis would be sufficient to explore the uncertainty around the base case results, and that the more complex probabilistic analysis was not considered applicable.

All cost parameters in the model (devices, procedures, follow-up, complications) were increased and decreased by 20% of their base-case value. Other model inputs (patient survival, device survival, complication rates, number of follow-up visits, warranty) were varied according to alternative clinical assumptions or literature findings.

Sensitivity analysis #1: Patient survival

There is no data on CRT-D patient survival in the UK. In the absence of UK-specific data, we have used an alternative data source in the sensitivity analysis rather than a range of values. Patient survival is an important variable in the model as it defines the number of patients *at risk* of a replacement.

Sensitivity analysis #2: Device survival

The device survival data in the base case relies on published evidence reported by [redacted][51]. Their analysis was the most appropriate as it is recent, is the largest cohort including 100% ENDURALIFE-powered CRT-Ds and provides independent observation of CRT-D batteries rather than battery projections.

New generation of devices are brought to market regularly by all device manufacturers aiming to provide clinicians and patients with devices offering improved features, programming and diagnostic capabilities, more comfortable shape, smaller size, and in some instances a genuine improvement in battery technology. A sensitivity analysis looking to address differences in battery performance between older and newer devices was recommended in the scope but very few options were available to us to perform this analysis:

(1) There is no published evidence available on any of the newest generation devices from competitors. The Boston Scientific CRT-Ds incorporating the ENDURALIFE battery technology were launched in 2008. We would have to wait a minimum of 6 years to obtain comparable independent evidence on the most recent generation devices (launched in 2016) from other manufacturers.

(2) In the absence of published evidence on device survival, the alternative data point is manufacturer-provided projected longevity figures included in most CRT-D Device Manuals. Projected service life ('battery longevity') estimates reported in these manuals depend on structural battery characteristics (chemistry and capacity) as well as utilisation criteria and programming settings (i.e., factors based on the patient's use of the device) which are unfortunately not consistent across the industry. Programming settings and criteria used to predict battery longevity can vary from very technical ones (e.g., pacing impedance in Ohms, Ω) to very relevant aspects to patient care such as the frequency of remote monitoring transmissions (i.e., the frequency at which the device will transmit device information to healthcare professionals remotely). This creates a very confusing environment for like-for-like comparisons. We attempted to re-calculate battery longevity from competitors' newest models using consistent programming settings and criteria as prescribed by a recent Decree from the French Haute Autorité de Santé[69]. However, there was not enough information in the device manuals to be able to carry out this like-for-like comparison.

(3) As the like-for-like comparison between manufacturers was not possible, we have instead carried out a more limited comparison of device models from the same manufacturer to estimate the percentage improvement in projected longevity for newest devices compared to the older generation devices included in the Landolina 2015[Error! Bookmark not defined.] cohort. We then applied this percentage improvement to the battery survival data used in the base case to effectively reset the survival probabilities from the base case to account for the increased longevity of the newest generation of devices. This analysis is considered relevant and appropriate as the same settings and criteria can be used to compare between different generations of devices by the same manufacturer.

We limited our analysis to Medtronic and St Jude Medical to align with the comparators used in the de novo cost analysis. We were not able to carry out

this analysis for St Jude Medical as their manuals do not publish their assumptions on device service life[70]. They advise that individual battery information should be collected at every individual device follow-up.

We replicated this analysis for ENDURALIFE-powered CRT-Ds in this as – while we have thus far conservatively assumed that all ENDURALIFE generation of devices had the same battery performance – continuous improvement in battery efficiency have allowed incremental improvement in projected battery longevity.

Medtronic launched their latest CRT-D devices – AMPLIA, COMPIA and CLARIA – in February 2016[71]. These devices were considered for the sensitivity analysis to reflect the newest generation devices. The older generation used for the comparison was Consulta, since the Landolina cohort included predominantly Consulta devices (see Appendix 3).

Table C19 shows the comparative projected longevity of these devices at various device programming settings. These figures have been used to calculate an estimated average improvement of the newest generation devices over the older generation.

Table C19 Medtronic projected longevity for older and newer generation devices

Device programming settings	Projected longevity (years)		Improvement
	Consulta[72]	**AMPLIA/CLARIA with AdaptivCRT**[(a)] [73,74]	
15% atrial, 100% BiV pacing, 6 months of pre-arrhythmia EGM, semi-annual shocks, 500 ohms, 2.5V/3.0V RA/RV & LV respectively, quarterly remote monitoring transmissions	5.6	6.5	+16%
5% atrial, 100% BiV pacing, 6 months of pre-arrhythmia EGM, semi-annual shocks, 500 ohms, 3.5V/4.0V RA/RV & LV respectively, quarterly remote monitoring transmissions	4.4	5.2	+18%
15% atrial, 100% BiV pacing, 6 months of pre-arrhythmia EGM, semi-annual shocks, 600 ohms, 2.5V/3.0V RA/RV & LV respectively, quarterly remote monitoring transmissions	5.9	6.8	+15%
15% atrial, 100% BiV, 6 months of pre-arrhythmia EGM, semi-annual shocks, 600 ohms, 3.5V/4.0V RA/RV & LV respectively, quarterly remote monitoring transmissions	4.7	5.5	+17%
Average improvement in projected longevity			**+17%**

(a) AdaptivCRT is a proprietary feature which adjusts CRT parameter values automatically while the patient is ambulatory. Figures in the table include longevity projections with AdaptivCRT as they are superior. Note that COMPIA does not include AdaptivCRT.

Boston Scientific's latest generation devices are the AUTOGEN/INOGEN/DYNAGEN/ORIGEN families (see section 4.2). The older generation used for the comparison was COGNIS, since the Landolina cohort included predominantly COGNIS devices (see Appendix 3). Table C20 shows the comparative projected longevity of these devices at various device programming settings. These figures have been used to calculate an estimated average improvement of the newest generation devices over the older generation.

Table C20 Boston Scientific projected longevity for older and newer generation devices

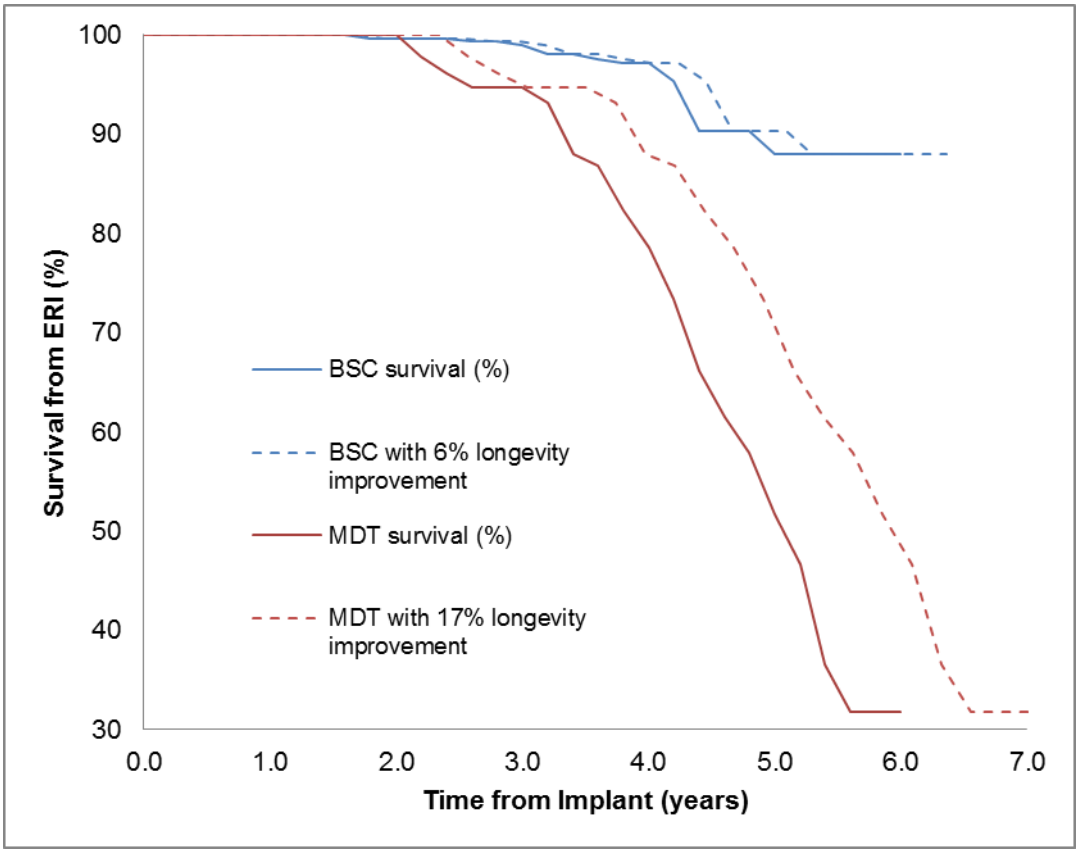
Device programming settings	Projected longevity (years)		Improvement
	COGNIS[75]	**AUTOGEN/DYNAGEN /ORIGEN/INOGEN[76]**	
15% atrial, 100% BiV pacing, 500 Ohms, 2.5V/3.0V RA/RV and LV respectively, EGM Onset ON[(a)(b)]	7.7	8.1	+5%
15% atrial, 100% BiV pacing, 500 Ohms, 3.5V/3.5V RA/RV and LV respectively, EGM Onset ON[(a)(b)]	6.5	6.8	+5%
15% atrial, 100% BiV pacing, 700 Ohms, 2.5V/3.0V RA/RV and LV respectively, EGM Onset ON[(a)(b)]	8.1	8.6	+6%
15% atrial, 100% BiV pacing, 700 Ohms, 3.5V/3.5V RA/RV and LV respectively, EGM Onset ON[(a)(b)]	6.9	7.5	+9%
Average improvement in projected longevity			**+6%**

(a) For COGNIS: 5 maximum energy charging cycles per year. Assumes standard use of the LATITUDE Communicator (remote management) as follows: Daily Device Check on, Weekly Device Alert on, weekly scheduled remote follow-ups, and quarterly patient-initiated interrogations

(b) For AUTOGEN: 3 maximum energy charging cycles per year. Assumes standard use of the LATITUDE Communicator (remote management) as follows: Daily Device Check on, monthly Full Interrogations (scheduled remote follow-ups, and quarterly patient-initiated interrogations).

The average improvements in projected longevity from tables C19 and C20 above have been applied to the device survival probabilities used in the base case. The time intervals at which the device survival probabilities were recorded were reproduced assuming an increased longevity of 17% and 6% at each data point for Medtronic and Boston Scientific respectively. This allowed us to develop a revised survival curve based on the Landolina 2016 data as shown in Figure C3.

Figure C3 Base case and revised device survival probability for ENDURALIFE-powered CRT-Ds (BSC) and Medtronic CRT-Ds (MDT)



Despite the incremental battery longevity increase (6%) between COGNIS devices included in the Landolina 2015[Error! Bookmark not defined.] cohort and the latest generation of ENDURALIFE-powered CRT-Ds, we decided to keep the base case input for ENDURALIFE-powered CRT-Ds for the sensitivity analysis and use the revised survival probability for Medtronic only (see Table C19). This is a conservative decision.

Sensitivity analysis #3: Warranty – 100% eligibility and uptake

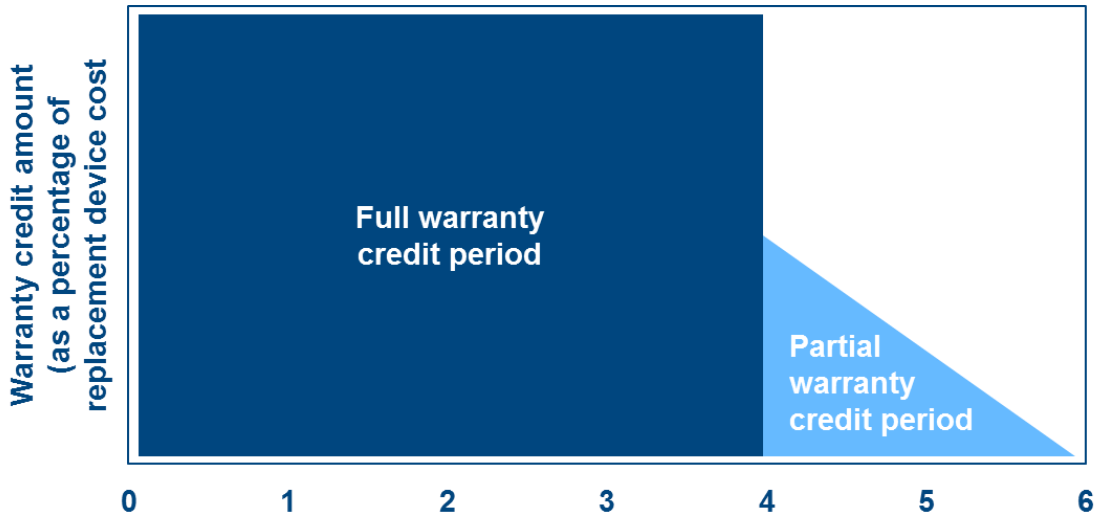
Warranty schemes are in place to credit hospitals when a patient needs to undergo a battery replacement before the warranty period ends. We have assumed that all

devices failing before year 6 reported in [redacted][51] – and used as the basis of our economic analysis – could be eligible under warranty schemes ('100% eligibility'). This is a conservative assumption as the conditions for the warranty payment to be granted are often restrictive and will differ across all manufacturers.

Since warranty schemes can vary according to manufacturer, for the purposes of the cost analysis, we have used the Boston Scientific warranty for CRT-D devices as a proxy for all comparators. The Boston Scientific warranty period for CRT-Ds is 6 years (4+2) which means that devices failing before 6 years are eligible for warranty payment. We are aware that some warranty schemes cover devices for a longer period however there is no public information available for all manufacturers and more generous schemes are generally available for only specific device models.

Boston Scientific's warranty provide for both full and prorated periods, expressed as a sum of two components – 4+2. The first component expresses the number of years during which devices failing due to early battery depletion will receive full warranty credit (i.e., a customer will receive a credit of 100% of the replacement unit). The second component indicates the pro-rata period during which the warranty credit decreases. This is shown graphically in Figure C4 below.

Figure C4 Warranty credit and proration



A standard warranty will apply the pro-ration on a daily basis. However, given the annual data points utilised in the cost analysis it is not possible to apply the warranty credits in this way. We have therefore assumed that any devices which do not survive to 5 years will receive the mid-point of the warranty credit for years 4 and 5. Similarly, for devices which do not survive to 6 years, the warranty credit is calculated

at the mid-point of years 5 and 6. Since warranties are only credited if the device is returned to the manufacturer and verified that they have functioned incorrectly, the sensitivity analysis varies the uptake of such warranties by the NHS to 100% (from a base case of 0% uptake).

Sensitivity analysis #4: Incidence of complications

Initial implantation and replacement of CRT-Ds carry a risk of complications – mainly infections, lead dislodgement or haematoma. The evidence around complications is fragmented and our assumptions in the base case analysis prioritised a conservative option (using the same rate of complications following initial or replacement procedures) and a trustworthy source of evidence[59].

It is nevertheless important to test this assumption in the sensitivity analysis. The literature review provided in Section 7.7 on adverse events identified a published systematic review on complications linked to replacement procedures. The sensitivity scenario is based on Lewis 2016[29].

Sensitivity analysis #5: number of routine annual follow-up visits

British guidelines on device monitoring[12] recommend 2 routine follow-up visits per year (at a minimum). However, the number of follow-ups can vary from hospital to hospital. We have accounted for this variation – with a lower value of 1 and a higher value of 3.

Sensitivity analysis #6: CRT-D device costs

The price was varied by +/- 20% for each manufacturer separately (one-way sensitivity analysis). This should reflect the price variation which can be observed in the NHS due to different contracts, volume agreements, service agreements and tier of devices.

Sensitivity analysis #7: Initial procedure costs

The price was varied by +/- 20% around the base case value.

Sensitivity analysis #8: Replacement procedure costs

The price was varied by +/- 20% around the base case value.

Sensitivity analysis #9: Complication costs

The price was varied by +/- 20% around the costs of complications used in the base case.

Sensitivity analysis #10: Follow-up costs

The price was varied by +/- 20% around the costs of follow-ups used in the base case.

10.2.3 Complete tables to summarise the variables used in the sensitivity analysis.

Table C21 Variables used in one-way scenario-based deterministic sensitivity analysis

<table>
<tr><th>Variable</th><th>Base-case value</th><th>Scenario value</th></tr>
<tr><td>#1 Patient survival</td><td>
<table>
<tr><th>Year of estimation</th><th>Patient survival[63]</th></tr>
<tr><td>0</td><td>100%</td></tr>
<tr><td>1</td><td>95%</td></tr>
<tr><td>2</td><td>90%</td></tr>
<tr><td>3</td><td>85%</td></tr>
<tr><td>4</td><td>81%</td></tr>
<tr><td>5</td><td>77%</td></tr>
<tr><td>6</td><td>72%</td></tr>
</table>
</td><td>
<table>
<tr><th>Year of estimation</th><th>Patient survival[77]</th></tr>
<tr><td>0</td><td>100%</td></tr>
<tr><td>1</td><td>90%</td></tr>
<tr><td>2</td><td>85%</td></tr>
<tr><td>3</td><td>80%</td></tr>
<tr><td>4</td><td>70%</td></tr>
<tr><td>5</td><td>65%</td></tr>
<tr><td>6</td><td>60%</td></tr>
</table>
</td></tr>
<tr><td>#2 Device survival</td><td>
<table>
<tr><th>Variable</th><th>MDT</th><th>STJ</th></tr>
<tr><td colspan="3">Cumulative probability of device survival[51]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td>
<table>
<tr><th>Variable</th><th>MDT</th><th>STJ</th></tr>
<tr><td colspan="3">Cumulative probability of device survival</td></tr>
<tr><td>Year 0</td><td>100%</td><td>n/a</td></tr>
<tr><td>Year 1</td><td>100%</td><td>n/a</td></tr>
<tr><td>Year 2</td><td>100%</td><td>n/a</td></tr>
<tr><td>Year 3</td><td>95%</td><td>n/a</td></tr>
<tr><td>Year 4</td><td>88%</td><td>n/a</td></tr>
<tr><td>Year 5</td><td>70%</td><td>n/a</td></tr>
<tr><td>Year 6</td><td>47%</td><td>n/a</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>#3 Warranty eligibility & uptake</td><td>0%</td><td>100%</td></tr>
<tr><td>#4 Rate of complication</td><td>
<table>
<tr><td colspan="2">Incidence of complications (de novo and replacement procedures)[59]</td></tr>
<tr><td>Infection</td><td>2.4%</td></tr>
<tr><td>Complication requiring re-intervention</td><td>8.5%</td></tr>
<tr><td>Device-pocket problem requiring revision</td><td>0.5%</td></tr>
</table>
</td><td>
<table>
<tr><td colspan="2">Incidence of complications (de novo and replacement procedures)[29(a)]</td></tr>
<tr><td>Infection</td><td>1.47%</td></tr>
<tr><td>Complication requiring re-intervention(b)</td><td>2.13%</td></tr>
<tr><td>Device-pocket problem requiring revision(c)</td><td>0.0%</td></tr>
</table>
(a) Stroke rate (0.45%) is not included in the sensitivity analysis as the base-case didn’t account for rate and cost of stroke.
(b) Include haematoma requiring re-intervention and other re-interventions.
(c) Not reported
</td></tr>
<tr><td>#5 Number of routine annual follow-up visits</td><td>2</td><td>Higher: 3
Lower: 1</td></tr>
<tr><td>#6 Device costs</td><td>Same price across manufacturers
£12,404 (initial implant)
£11,858 (replacement)</td><td>Higher: £14,884 (initial implant); £14,229 (replacement)
Lower: £9,923 (initial implant); £9,486 (replacement)</td></tr>
<tr><td>#7 Procedure costs (initial implant)</td><td>HRG EA56Z = £6,201</td><td>Higher: £7,441
Lower: £4,961</td></tr>
<tr><td>#8 Procedure costs (replacement)</td><td>EA12Z = £4,700</td><td>Higher: £5,640
Lower: £3,760</td></tr>
<tr><td>#9 Complication costs</td><td>
<table>
<tr><th>Adverse events</th><th>Value</th></tr>
<tr><td>Infection</td><td>£21,774</td></tr>
<tr><td>Complication requiring re-intervention</td><td>£6,152</td></tr>
<tr><td>Device-pocket problem requiring revision</td><td>£18,010</td></tr>
</table>
</td><td>
<table>
<tr><th>Adverse events</th><th>High</th><th>Low</th></tr>
<tr><td>Infection</td><td>£26,129</td><td>£17,419</td></tr>
<tr><td>Complication requiring re-intervention</td><td>£7,382</td><td>£4,291</td></tr>
<tr><td>Device-pocket problem requiring revision</td><td>£21,612</td><td>£14,408</td></tr>
</table>
</td></tr>
</table>

#10 Follow-up costs	£96	High: £115 Low: £77

10.2.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

It was not considered necessary to perform a sensitivity analysis on the variable relating to frequency of post-procedure follow-ups.

10.3 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

10.3.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis.

Our base case analysis reports two set of results:

- **Total cost per patient over 6 years** – the economic analysis 'follows' this one patient and their likelihood of having a replacement device over 6 years.

- **Total costs for the English NHS over 6 years** - **healthcare system budget impact** - the NHS analysis reports results for the overall CRT-D population (N = 3,031) in 2014/15[60]. It assumes that 3,031 more patients are implanted every year. This would represent a more realistic impact analysis for the NHS rather than following the same initial cohort for 6 years.

Table C22 Base-case results – per patient

	Total per patient cost
ENDURALIFE-powered CRT-Ds (Boston Scientific)	£22,322
Medtronic CRT-Ds	£29,158
St Jude Medical CRT-Ds	£27,309

Table C23 Base-case results – population based on 3,031 CRT-D implants per year over 6 years

	Total costs replacement procedures	Total number of replacement procedure
ENDURALIFE-powered CRT-Ds (Boston Scientific)	£10.4 million	698
Medtronic CRT-Ds	£54.5 million	3,656
St Jude Medical CRT-Ds	£28.4 million	1,934

10.3.2 Report the total difference in costs between the technology and comparator(s).

Table C24 Difference in cost per patient

	Total per patient cost	Difference to BSC	Difference to BSC (%)
ENDURALIFE-powered CRT-Ds (Boston Scientific)	£22,322	-	-
Medtronic CRT-Ds	£29,158	+£6,836	+31%
St Jude Medical CRT-Ds	£27,309	+£4,986	+22%

The cost per patient increases between +22% and +31% when a device without the ENDURALIFE battery technology is considered compared to Boston Scientific ENDURALIFE-powered CRT-D.

Table C25 Base case results – population based on 3,031 CRT-D implants per year over 6 years

	Total costs replacement procedures	Difference	Total number of replacement procedures	Difference
ENDURALIFE-powered CRT-Ds (Boston Scientific)	£10.4 million		698	
Medtronic CRT-Ds	£54.5 million	+ £44.1 million	3,656	2,959
St Jude Medical CRT-Ds	£28.4 million	+ £18.1 million	1,934	1,236

The difference in longevity between manufacturers means the NHS could save up to £44 million over 6 years and free up capacity to treat up to 2,959 new patients (instead of replacing devices previously implanted).

10.3.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table C26

Table C26 Total costs per patient over 6 years by category

	ENDURALIFE-powered CRT-Ds (Boston Scientific)	Medtronic CRT-Ds	St Jude Medical CRT-Ds	Difference MDT vs BSC	% MDT vs BSC	Difference STJ vs BSC	% STJ vs BSC
Initial implant costs	**£19,836**	**£19,836**	**£19,836**	**-**	**-**	**-**	**-**
Devices	£12,404	£12,404	£12,404	-	-	-	-
Procedures	£6,201	£6,201	£6,201	-	-	-	-
Complications	£1,136	£1,136	£1,136	-	-	-	-
Post-procedure follow-ups	£96	£96	£96	-	-	-	-
Replacement costs (6 years)	**£1,437**	**£8,273**	**£6,423**	**+£6,836**	**476%**	**+£4,986**	**347%**
Devices	£958	£5,514	£4,281	+£4,557	476%	+£3,324	347%
Procedures	£380	£2,186	£1,697	+£1,806	476%	+£1,317	347%
Complications	£92	£528	£410	+£436	476%	+£318	347%
Post-procedure follow-ups	£8	£45	£35	+£37	476%	+£27	347%
Routine follow-up (6 years)	**£1,049**	**£1,049**	**£1,049**	**-**	**-**	**-**	**-**
TOTAL	**£22,322**	**£29,158**	**£27,309**	**+£6,836**	**31%**	**+£4,986**	**22%**

The costs of the initial implant are equal for all manufacturers. The savings are realised in subsequent years with the reduction in the costs associated with replacement procedures (admission + consumables + follow-up) and associated complications.

10.3.4 If appropriate, provide details of the costs for the technology and its comparator by health state.

Not appropriate

10.3.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event.

See complications in Table C26 in section 9.5.3 above.

Sensitivity analysis results

10.3.6 Present results of deterministic one-way sensitivity analysis of the variables.

Results from the deterministic one-way sensitivity analysis is presented separately below for Medtronic versus ENDURALIFE-powered CRT-Ds (Boston Scientific) and St Jude Medical vs ENDURALIFE-powered CRT-Ds (Boston Scientific).

Figure C5 Results of deterministic univariate analysis: Difference in cost per patient between Medtronic vs ENDURALIFE-powered CRT-Ds (Boston Scientific)

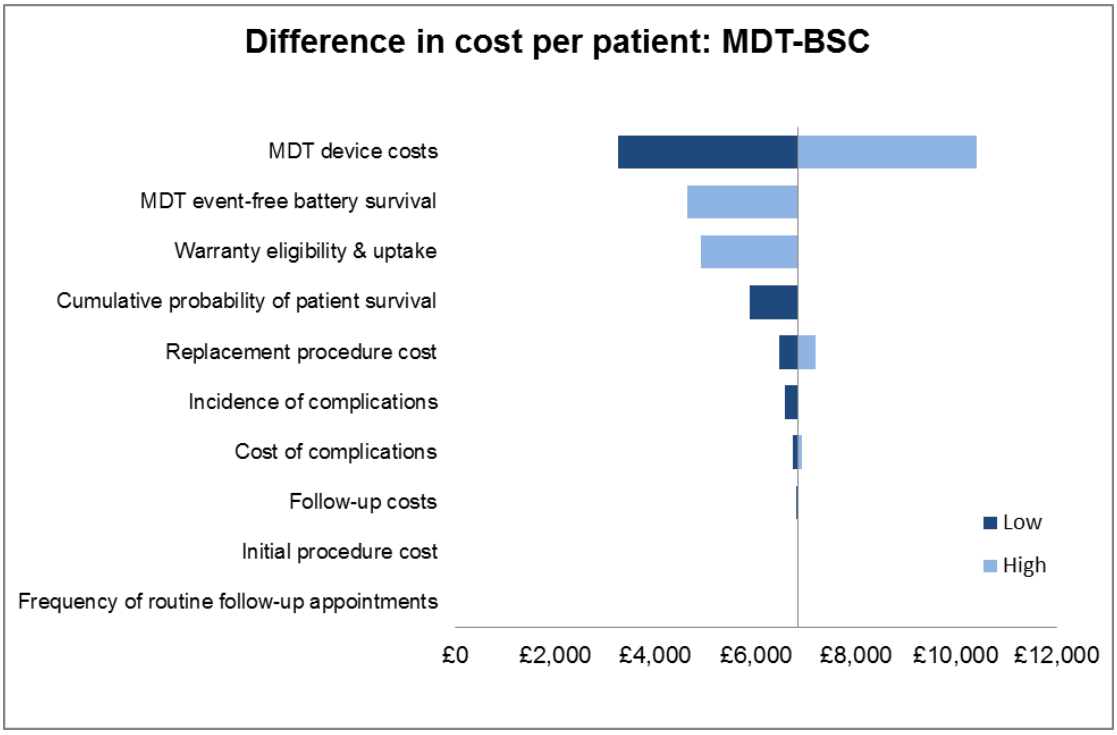


Table C27 Results of deterministic univariate analysis: Difference in cost per patient between Medtronic vs ENDURALIFE-powered CRT-Ds (Boston Scientific)

	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

Figure C6 Difference in cost per patient between St Jude Medical vs ENDURALIFE-powered CRT-Ds (Boston Scientific)

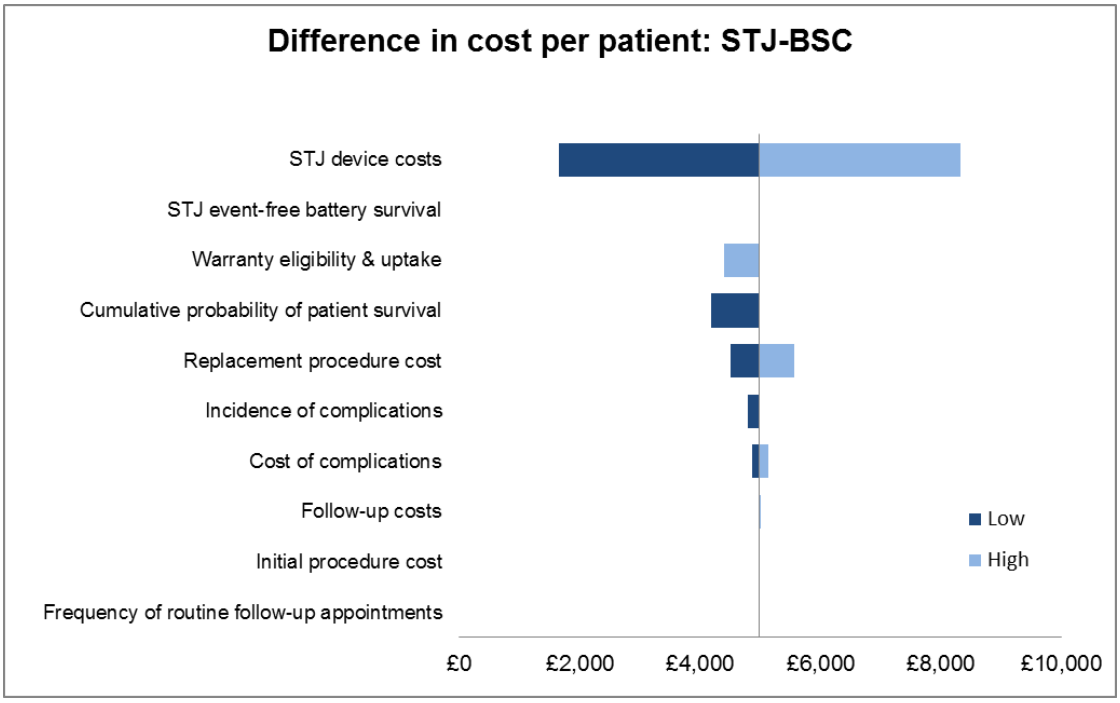


Table C28 Results of deterministic univariate analysis: St Jude Medical vs ENDURALIFE-powered CRT-Ds (Boston Scientific)

	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

10.3.7 Present results of deterministic multi-way scenario sensitivity analysis.

Not available

10.3.8 Present results of the probabilistic sensitivity analysis.

Not applicable.

10.3.9 What were the main findings of each of the sensitivity analyses?

All sensitivity analyses carried out supported the conclusion of the base case analysis, namely that ENDURALIFE-powered CRT-Ds are cost-saving versus

comparator CRT-Ds. Further details on each sensitivity analysis carried out can be found below.

Sensitivity analyses #1: Patient survival

Overall cost per patient – and relative savings – are sensitive to patient survival assumptions, as they define the number of patients at risk of having a replacement. However, this parameter has a limited impact on the relative cost difference between ENDURALIFE-powered CRT-Ds and comparator CRT-Ds.

Sensitivity analysis #2: Device survival

A CRT-D device is designed to deliver life-saving therapy to patients. As such, when the battery on a device depletes to the extent where it can no longer deliver this therapy, it must be replaced. Given the direct correlation between device survival and the need for implantation of a replacement device, this parameter has a considerable impact on the relative cost differences between technologies – with higher device survival resulting in a marked decrease in relative costs.

Sensitivity analysis #3: Warranty uptake of 100%

The sensitivity analysis around warranty uptake is essentially measuring the impact of variation in device price, since the healthcare system will be reimbursed part or all of the cost of device under a warranty should it deplete earlier than expected. Given the significance of device price in the cost analysis, the results are quite sensitive to changes in this parameter.

Sensitivity analysis #4 & 9: Incidence and cost of complications

While it is clear complications can have a significant impact on patients' quality of life, the sensitivity analysis demonstrated that in the context of overall cost burden the incidence and cost of such complications have a limited impact.

Sensitivity analysis #5 & 7: Frequency of routine annual follow-up visits and initial procedure cost

While initial procedure costs and, to a lesser degree, frequency of routine annual follow-up visits have an impact on overall cost per patient, these parameters affect ENDURALIFE-powered CRT-Ds and competitor CRT-Ds to the same degree in the

cost per patient analysis and hence have no impact on the relative cost differences between these technologies.

Sensitivity analysis #6: CRT-D device costs

The cost model is highly sensitive to changes in device costs. The sensitivity to CRT-D device cost is higher than that of warranty due to the pro-rata nature of warranties (as detailed in section 9.4.2).

Sensitivity analysis #8: Replacement procedure costs

Replacement procedure costs have an impact on the relative cost difference between manufacturers, albeit limited compared to other parameters described above.

Sensitivity analysis #10: Follow-up costs

Follow-up costs are not a significant contributor to the overall cost per patient, and as such, their impact on the relative cost savings between technologies is negligible.

10.3.10 What are the key drivers of the cost results?

The sensitivity analyses identified that the 2 main drivers of the cost results are device cost and device survival.

Miscellaneous results

10.3.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

While the sensitivity analysis results in section 9.5.10 above focused on the impact on relative cost per patient of technologies, it is important to note the overall implication to patients and the healthcare system which cannot be offset with as much ease as costs.

For example, while device cost and warranty have been shown to have a considerable impact on relative costs between technologies, these parameters do not have any effect on the number of invasive procedures that patients may have to face as a result of a device whose battery is expiring.

To address this concern, we have used the cost model to perform a simple analysis on the number of admissions for invasive procedures that a single CRT-D patient may face over six years, assuming a single admission – for each initial or replacement procedure or complication requiring an intervention. The results are presented below in Table 29.

Table C29 Number of admissions per patient over 6 years by category

	ENDURALIFE-powered CRT-Ds (Boston Scientific)	Medtronic CRT-Ds	St Jude Medical CRT-Ds
Initial implant procedure	1.00	1.00	1.00
Replacement procedure	0.09	0.55	0.44
Complications requiring revision	0.12	0.18	0.16
TOTAL	**1.22**	**1.72**	**1.60**

10.4 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

10.4.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

No subgroups were identified in the scope and as such, no subgroup analysis was undertaken as part of the de novo cost model.

10.4.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

10.4.3 Describe how the subgroups were included in the cost analysis.

Not applicable.

10.4.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Not applicable.

10.4.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

10.5 Validation

10.5.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Robust internal and external quality assurance with multiple rounds of review was performed to ensure that the model performs as intended.

10.6 Interpretation of economic evidence

10.6.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of the de novo cost analysis are consistent with the published economic literature. The published economic literature presented in section 8 clearly shows the link between device battery longevity and overall costs and the significant impact of a longer battery life on reducing healthcare costs. Methodologies adopted in the economic literature vary and only [redacted] use device probability of survival rather than a point estimate of device longevity. The de novo cost analysis demonstrated that the difference in total cost per patient over 6 years ranged between 31% (Medtronic vs ENDURALIFE-powered CRT-Ds) and 22% (St Jude Medical vs ENDURALIFE-powered CRT-Ds). It also demonstrated a difference of + 476% and + 347% in replacement costs respectively. These results are consistent with the literature:

[redacted]

10.6.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes. As described above the cost analysis is in line with the patient population identified in the scope (all patients indicated for and receiving a CRT-D).

The base-case also presents the results for all CRT-D patients implanted in England.

10.6.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The main strength of the analysis resides in the utilisation of published clinical data on device battery survival rather than battery projections from manufacturers. Battery longevity estimates reported in product manuals depend on intrinsic battery characteristics (chemistry, capacity and efficiency) as well as utilisation criteria and settings which are unfortunately not consistent across the Industry. This creates a somewhat confusing environment for like-for-like comparison and has thankfully been clarified by recent independent studies comparing battery survival by manufacturers.

The main weakness of the analysis resides in the difference of device models used in the published literature compared to models and technologies currently available on the market. NICE requested that uncertainties around battery performance between older and newer devices were investigated, which we have tried to address through sensitivity analysis but there remains a lack of high quality comparable data for newer generation devices.

The de novo cost model uses clinical data published in 2015. It provides information on device survival up to 6 years – however the size of the sample available at Year 6 is small which is a limitation of our analysis.

10.6.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

We are aware of an ongoing analysis being conducted based on the UK British Heart Rhythm Society/NICOR Cardiac Rhythm Management National Clinical Audit registry focusing on device longevity. The availability of UK specific device longevity based on large patient umbers would enhance the robustness and relevance of our results. We are unclear as to the progress of this analysis nor the publication plans and therefore cannot confirm when this may become available.

10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library

Pubmed was the primary database searched. Furthermore, Cochrane and ClinicalTrials.gov were searched.

10.1.2 The date on which the search was conducted.

This review was conducted on 4 May 2016.

10.1.3 The date span of the search.

From 2008 to 2016 (last access: 4 May 2016)

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean)

Source	Search Criteria	Exclusion criteria
PubMed	(longevity OR lifespan OR replacement OR drain) AND (cardioverter OR defibrillator OR icd OR crt OR resynchronization OR resynchronisation OR cardiac device*) AND battery 2008:2016[dp]	Articles published prior to January 1st 2008
Cochrane	(longevity OR lifespan OR replacement OR drain) AND (cardioverter OR defibrillator OR icd OR crt OR resynchronization OR resynchronisation OR cardiac device) AND battery	
ClinicalTrial.gov		
Hand-searching	Analysis of internal company documentation	

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

A literature search was conducted using three main sources of clinical evidence (Pubmed, Cochrane, ClinicalTrials.gov). The evidence not indexed but included in the present submission was retrieved from an analysis of Boston Scientific libraries, collecting abstracts, congress presentations and other external communications in the area of cardioverter defibrillators.

10.1.6 The inclusion and exclusion criteria.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Patients implanted with CRT-Ds
Interventions	• ENDURALIFE-powered CRT-Ds (Boston Scientific)
Outcomes	Device and battery survival/longevity; time to reaching ERI; predictors of battery survival
Study design	All studies (conducted in experimental or observational setting) comparing CRT-D outcomes by technology/manufacturer and evaluating the ENDURALIFE Battery Technology
Language restrictions	English language only
Other restrictions	Full text or abstract available
Search dates	Articles published between 2008 and 2016

Exclusion criteria	
Population	Patients implanted exclusively with ICDs (i.e. ICD-VR, ICD-DR, not CRT-Ds)
Interventions	Studies where: - ENDURALIFE-powered CRT-Ds represented less than 50% of the overall BSC implanted CRT-D devices, AND/OR the proportion of ENDURALIFE-powered CRT-Ds was not clearly reported AND/OR - A subgroup analysis on ENDURALIFE-powered CRT-Ds was not conducted
Outcomes	-
Study design	Non-comparative studies/editorials/reviews
Language restrictions	English language only
Other restrictions	No full text or abstract available
Search dates	Articles published prior to 2008 (antecedent to the date of market authorisation of the first ENDURALIFE-powered CRT-D device)

10.1.7 The data abstraction strategy.

Tables were created with defined headings corresponding to relevant data to be extracted. Articles were manually searched for the information under each heading and this data was abstracted accordingly.

10.2 Appendix 2: Excluded articles and criteria for exclusion (section 7.2.2)

Table B2 Excluded articles and criteria for exclusion

Study name (acronym)	Primary study reference	Population	Intervention	Comparator	Exclusion criteria
Dechert 2016[78]	Implantable Cardioverter Defibrillator Outcomes in Pediatric and Congenital Heart Disease: Time to System Revision	Patients implanted with ICDs	Boston Scientific	• Medtronic • St. Jude	No CRT-D included in the analysis
Denman 2016[79]	The time to elective replacement of BV implantable defibrillators: manufacturers are not created equal?	Patients implanted with BV ICDs	Boston Scientific	Medtronic	ENDURALIFE-powered devices <50%
Zanon 2016[80]	Device Longevity in a Contemporary Cohort of ICD/CRT-D Patients Undergoing Device Replacement SHORT TITLE: Longevity of replaced ICD/CRT-D	Patients implanted with CRT-Ds or ICDs	Boston Scientific	• Medtronic • St. Jude • Biotronik • Sorin	ENDURALIFE-powered devices <50%
Seegers 2015[81]	Longevity of implantable cardioverter-defibrillators in a single-center population	Patients implanted with CRT-Ds or ICDs	Boston Scientific	• Medtronic • Biotronik	ENDURALIFE-powered devices <50%
Jakub 2015[82]	Re-implantation surgery in patients with implantable cardioverter defibrillators: A qualitative study	Patients implanted with ICDs	-	-	Lack of quantitative findings

Din 2016[83]	Does ICD longevity vary by manufacturer?	Patients implanted with ICDs or CRT-Ds	Boston Scientific	Medtronic	Proportion of ENDURALIFE-powered devices not available
Johansen 2014[84]	Device longevity in cardiac resynchronization therapy implantable cardioverter defibrillators differs between manufacturers	Patients implanted with CRT-Ds	Boston Scientific	• Medtronic • St. Jude • Biotronik	Proportion of ENDURALIFE-powered devices not available
Thijissen 2012[85]	Implantable cardioverter-defibrillator longevity under clinical circumstances: an analysis according to device type, generation, and manufacturer	Patients implanted with CRT-Ds or ICDs	Boston Scientific	• Medtronic • St. Jude • Biotronik	Proportion of ENDURALIFE-powered devices not available

Note: for the studies highlighted in grey, the evaluation of the proportion of ENDURALIFE-powered devices was still on going at the time of submission. These articles might have included relevant information for the present submission; however, due to the uncertainty on inclusion criteria they have been excluded.

10.3 Appendix 3: Details on models included, for each manufacturer, in the articles evaluated for the present review

The table reported below shows, for each manufacturer, all the models included in the studies evaluated for the present review.

	Biotronik	Boston Scientific	Cameron Health	Intermedics	Medtronic	St Jude Medical	Sorin
Alam 2016 **N= 621**	0	H210 Contak Renewal 3 RF (10) H217 Contak Renewal 3 RF HE (3) H219 Contak Renewal 3 RF HE (1) H220 LIVIAN (16) H225 LIVIAN (2) H227 LIVIAN HE (18) H229 LIVIAN HE (16) *N118 COGNIS 100-D (22)* *N119 COGNIS 100-D (100)* **Total (188)** ***ENDURALIFE-powered CRT-Ds (122)***	0	0	**Total (391)**	3207-30 (3) 3207-36 (37) 3211-36 (1) 3211-36Q (1) CD3211-36 (14) CD3215-36Q (1) **Total (57)**	0
Ellis 2016[(a)] **N= 1,302**[(b)]	0	LIVIAN (8) Renewal 3 RF (2) *ENDURALIFE-Cognis (311)* *ENDURALIFE-Energen/Incepta (1)* **Total (322)** ***ENDURALIFE-powered (312)***	0	0	InSync Maximo (20) Concerto (229) Consulta (542) Protecta (1) **Total (792)**	Promote (134) Promote Quadra (1) Promote Quadra Assura (1) Unify (47) Unify Assura (3) **Total (186)**	0
Landolina 2015 **N= 1,726**	Lumax 300 (3) Lumax 340 (26) Lumax 540 (20) **Total (49)**	LIVIAN (29) RENEWAL (288) *COGNIS (291)* **Total (608)** ***ENDURALIFE-powered (291)***	0	0	InSync III Marquis (67) InSync Maximo (21) InSync Sentry (7) Maximo II (69) Concerto (171) Consulta (447) Protecta (16) **Total (798)**	Atlas (40) Epic (26) Promote (106) **Total (172)**	Ovatio (30) Paradym/Paradym RF (69) **Total (99)**
Lau 2015 **N= 155**	0	*COGNIS (27)* **Total (27)** ***ENDURALIFE-powered (27)***	0	0	unspecified (62) **Total (62)**	Unspecified (66) **Total (66)**	0
Von Gunten 2015 **N= 4,881**	Belos VR-T (22) Ilesto 7 CRT (1) Ilesto 7 VRT (19) Kronos LV-T (3) Lexos A+/T (16) Lexos DR-T (25) Lexos VR-T (56) Lumax 300 DR-T (11) Lumax 300 VR-T (67)	Contak CD 1823 (11) Contak Renewal 2 H155 (30) Contak Renewal 4 190 (1) Contak Renewal 4 AVT M177 HE (23) Contak Renewal 4 H195 (15) Contak Renewal 4 HE H199 (14) Contak Renewal 4 RF H230 (31) Contak Renewal 4 RF H235 (9) Contak Renewal H135 (21)	1010 SQ-RX (99)	Micron (7) ResQ micron (14)	Concerto C 174 (52) Consulta D234TRK (23) Entrust DDD (4) Entrust VVI (32) Evera (1) Evera XT DR (1) GEM 7227 (56) GEM II 7271 (1) GEM II DR 7271 (32)	Atlas DR V-240 (59) Atlas DR V-243 (62) Atlas HF V-341 (100) Atlas II DR V-268 (59) Atlas II VR V-168 (105) Atlas II+ HF V-367 (143) Atlas V-366 (1) Atlas VR V-193 (103) Atlas VR V-199 (72)	Alto DR 614 (28) Alto DR 624 (3) Defender IV DR 612 (15) Ovatio DR-6550 (56) Ovatio VR-6250 (5) Paradym 8250 (5) Paradym 8550 (14) Paradym 8750 (2) Paradym 8758 (1)

	Lumax 340 DR-T (14) Lumax 340 HF-T (30) Lumax 340 VR-T (42) Lumax 540 DR-T (106) Lumax 540 HF-T (148) Lumax 540 VR-T (259) Lumax 740 DR-T (24) Lumax 740 HF-T (46) Lumax 740 VR-T (82) Lumos DR-T (28) Lumos VR-T (82) Phylax AV (49) Tachos Atx (42) Tachos DR (44) Xelos DR-T (3) **Total (1,219)**	Teligen CRT (2) Teligen DR (28) Teligen VR (82) Ventak Mini 4 1793 (34) Ventak Prizm 1850 (4) Ventak Prizm 2 1851 (9) Ventak Prizm 2 1860 (35) Ventak Prizm 2 1861 (46) Ventak Prizm AVT 1900 (5) Ventak Prizm HE 1852 (28) Ventak Prizm HE 1853 (22) Vitality 1871 (65) Vitality 2 EL 167 (9) Vitality 2 EL T177 (48) Vitality 2 T165 (77) Vitality 2 T175 (142) Vitality A 155 (3) Vitality VR 1870 (12) *Cognis CRT (76)* *Energen CRT (24)* Energen DR (9) Energen VR (28) Incepta F 162 (2) Incepta P 163 (1) Incepta P 165 (1) **Total (947)** **Total CRT-Ds (257)** ***ENDURALIFE-powered (102)***	**Total (99)**	**Total (21)**	GEM II DR 7273 (1) GEM II VR 7229 (4) GEM III 7231 (88) GEM III 7275 (15) GEM III 7276 AT (9) InSync 7272 (25) InSync III Marquis 7279 (47) InSync Sentry 7298 (46) Intrinsic 7288 (17) Jewel 7219 (9) Jewel 7220 (4) Jewel 7221 (1) Jewel AF 7250 H (19) Marquis 7230 VR (50) Marquis 7274 DR (39) Maximo 7232 (18) Maximo 7278 (5) Microjewel 7221 (8) Microjewel 7223 (7) Protecta CRT (63) Protecta DDD (13) Protecta VVI (68) Secura DDD (1) Secura VVI (26) Virtuoso D154AWG DR (26) Virtuoso D154VWC VR (77) Viva-Q VT (10) **Total (898)**	Contour V 175 (1) Current DR 2215 (4) Current RF 1207 (84) Current RF 2207 (47) Current VR 1215 (5) Ellipse CD 1277 (59) Ellipse CD 1377 (18) Ellipse CD 2277 (48) Ellipse CD 2377 (16) Epic HF V-339 (19) Epic V-158 (4) Fortify CD 1233 (138) Fortify CD 2233 (93) Fortify CD 2259 (1) Photon micro 194 (9) Photon micro 232 (1) Photon V 194 (1) Photon V-230 (3) Profile 186 (20) Promote 3215 (1) Promote Quadra (1) Promote RF 3213 (104) Unify Assura CD 3261 (29) Unify Assura CD 3361 (6) Unify CD 3235 (1) Unify CD 3235 (118) Unify CD 3251 (2) Ventritex 190 (2) **Total (1,539)**	Paradym 9550 (28) Paradym SonR 9770 (1) **Total (158)**
Alam 2014 **N=646**	0	H210 Contak Renewal 3 RF (10) H217 Contak Renewal 3 RF HE (3) H219 Contak Renewal 3 RF HE (1) H220 LIVIAN (16) H225 LIVIAN (2) H227 LIVIAN HE (18) H229 LIVIAN HE (16) *N118 COGNIS 100-D (22)* *N119 COGNIS 100-D (100)* **Total (188)** ***ENDURALIFE-powered (122)***	0	0	8042 InSync III (6) D284TRK Maximo II CRT-D (3) C154DWK Concerto (178) C154VWC Concerto (1) D224TRK Consulta (227) D274TRK Concerto II (1) **Total (416)**	3207-30 (3) 3207-36 (37) 3211-36 (1) 3211-36Q (1) CD3211-36 (14) CD3215-36Q (1) **Total (57)**	0

Williams 2014[(a)] **N=91**	0	LIVIAN (1) Renewal 3 RF (1) *ENDURALIFE-Cognis (51)* **Total (53)** ***ENDURALIFE-powered (51)***	0	0	Maximo II (26) InSync Maximo (1) Concerto (1) **Total (28)**	Promote (7) Promote Accel (3) **Total (10)**	0

(a) Details on device models obtained from personal communications from Dr Ellis and Dr Williams, May 2016

(b) The total number of implants is N=1,302 in the published article. However the detailed information on model types is available on 1,300 implants only.

10.4 Appendix 4: Critical appraisal of observational studies (section 7.5.1)

Table B8.1 Critical appraisal of observational studies - Alam 2016

Study name: Alam 2016[15]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	• Device replacement (for battery reaching elective replacement indicator) is an objective indicator • Device replacements for battery depletion were counted as failures, in line with the purpose of this study • Patients were censored at the time of death, device replacement for infection, device or lead malfunctions, or removal at the time of heart transplantation • 94 were excluded from the analysis because they were lost to follow-up within a month of device implantation • Survival analysis methodology ensured comparability among treatment groups
Have the authors identified all important confounding factors?	Yes	The authors considered that the small sample size in the Biotronik group could affect robustness of the comparison vs other CRT-D devices
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	• Biotronik devices were excluded from the analysis as 6 devices only were produced by this manufacturer and that should have precluded meaningful comparison • Author declared to have adjusted for unbalanced electrical pacing parameters between devices from different manufacturers

Was the follow-up of patients complete?	No	• N=94 patients were excluded from the analysis because they were lost to follow-up within a cohort of 721 patients • Remaining patients were followed-up until the date of event or last outpatient follow-up (for this information, the authors refer to Alam 2014) • However, incomplete follow-up is common in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values were provided for all the results
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.2 Critical appraisal of observational studies - Ellis 2016

Study name: Ellis 2016[16]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	• Device replacement (for battery reaching elective replacement indicator) is an objective indicator • Device replacements for battery depletion were counted as failures, in line with the purpose of this study • Patients were censored if the replacement was due to non-depletion reasons or death • Survival analysis methodology ensured comparability among treatment groups
Have the authors identified all	Not clear	• Survival analysis methodology ensured

important confounding factors? **Have the authors taken account of the confounding factors in the design and/or analysis?**		comparability among treatment groups • Analysis of patients' characteristics and device parameters were conducted • Multivariate analysis was not conducted
Was the follow-up of patients complete?	Not clear	Incomplete follow-up is common in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Not clear	P value was provided for survival (i.e. longevity) analyses only
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.3 Critical appraisal of observational studies - Landolina 2015

Study name: Landolina 2015[17]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	• Device replacement (for battery reaching elective replacement indicator) is an objective indicator • Device replacements for battery depletion were counted as failures, in line with the purpose of this study • Survival analysis methodology ensured comparability among treatment groups • 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 • Authors performed univariate and multivariate regressions in order to conduct

		adjusted analysis
Have the authors identified all important confounding factors?	Yes	Authors performed univariate and multivariate regressions in order to conduct adjusted analysis
Have the authors taken account of the confounding factors in the design and/or analysis?		
Was the follow-up of patients complete?	Not clear	However, incomplete follow-up is common in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values were reported for all the comparisons and for beta coefficients in regression analyses
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.4 Critical appraisal of observational studies - Lau 2015

Study name: Lau 2015[18]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	• Device replacement (for battery reaching elective replacement indicator) is an objective indicator • Device replacements for battery depletion were counted as failures, in line with the purpose of this study • Non-ERI events removing devices from service were censored • Survival analysis methodology ensured

		comparability among treatment groups
Have the authors identified all important confounding factors? **Have the authors taken account of the confounding factors in the design and/or analysis?**	Not clear	• Survival analysis methodology ensured comparability among treatment groups • Analysis of patients' characteristics, aimed to analyse potential confounding factors was not mentioned in the publication; there is no proof it was conducted
Was the follow-up of patients complete?	Not clear	However, incomplete follow-up is common in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Authors reported p values for the comparison among 3 groups and for pairwise comparisons
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.5 Critical appraisal of observational studies - von Gunten 2015

Study name: von Gunten 2015[19]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	• Device replacement (for battery reaching elective replacement indicator) is an objective indicator • As all CRT-Ds implanted in both centres were included over a long period of time (1994-2014), some results could be not representative of the longevity of currently available CRT-Ds. To overcome this issue authors performed stratified analysis (implantation prior to 2006, and after 2006) • Device replacements for battery

		depletion were counted as failures, in line with the purpose of this study • All other replacement events due to upgrade or removal for infection were censored at the date of the procedure • All patient adverse events, such as death, heart transplantation, etc. were censored at the date of these corresponding events • Implantable CRT-Ds still in service were censored at the date of last database access • Survival analysis methodology ensured comparability among treatment groups
Have the authors identified all important confounding factors? **Have the authors taken account of the confounding factors in the design and/or analysis?**	Not clear	• Stratified analysis was conducted to analyse longevity by device generation (implantation prior to 2006, and after 2006) • Other confounding related to patients' characteristics were not analysed, due to the lack of information for the majority of implanted devices
Was the follow-up of patients complete?	Not clear	However, incomplete follow-up is common in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values were provided for all the survival analyses
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.6 Critical appraisal of observational studies - Alam 2014

Study name: Alam 2014[20]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	• Device replacement (for battery reaching elective replacement indicator) is an objective indicator • Device replacements for battery depletion were counted as failures, in line with the purpose of this study • Patients were censored at the time of death, device replacement for infection, device or lead malfunctions, or removal at the time of heart transplantation • Patients were followed to the date of event or last outpatient follow-up • Survival analysis methodology ensured comparability among treatment groups
Have the authors identified all important confounding factors?	Yes	The authors considered that the small sample size in the Biotronik group could affect robustness of the comparison vs other CRT-D devices
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	• Data collected with the same frequency from each manufacturer (once every 3 months) were used • Biotronik devices were excluded from the analysis as they observed 6 devices only produced by this manufacturer and that should have precluded meaningful comparison
Was the follow-up of patients complete?	No	• N=94 patients (within a cohort of 646) were lost to follow-up and excluded from the analysis • Remaining patients were followed-up until the date of event or last outpatient follow-up • However, incomplete follow-up is common

		in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values were provided for all the results
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table B8.7 Critical appraisal of observational studies - Williams 2014

Study name: Williams 2014[21]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	• The cohort recruited in the analysis was representative of the patient population to investigate (i.e. subjects implanted with CRT-D) • No exclusion criteria biasing results (i.e. favouring/disfavouring either ENDURALIFE-powered CRT-Ds/BSC or alternative technologies) were found
Was the exposure accurately measured to minimise bias?	Yes	• The study was not affected by exposure bias • Treatment with CRT-D is an objective measurement; patients were all CRT-D implanted (100% exposure)
Was the outcome accurately measured to minimise bias?	Yes	Device replacement (for battery reaching elective replacement indicator) is an objective indicator
Have the authors identified all important confounding factors?	Yes	• Survival analysis methodology ensured comparability among treatment groups • Authors conducted Cox regression analyses to evaluate the effect of confounding factors
Have the authors taken account of the confounding factors in the design and/or analysis?		
Was the follow-up of patients complete?	Not clear	However, incomplete follow-up is common in retrospective observational studies; survival analysis techniques ensure validity of results in presence of incomplete follow-up
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values were reported for survival analyses and device parameters by manufacturer comparison
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

10.5 Appendix 5: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.5.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

Pubmed was the primary database searched.

10.5.2 The date on which the search was conducted.

This review was conducted on April 28th 2016.

10.5.3 The date span of the search.

No data restriction.

10.5.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Source	Search Criteria
Pubmed	(cardioverter OR defibrillator OR icd OR crt OR resynchronization OR resynchronisation OR cardiac device*) AND replacement
Hand-searching	Analysis of internal company documentation

10.5.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The literature search was conducted using Pubmed as the main source of clinical evidence. The unindexed evidence included in the present submission was retrieved from an analysis of Boston Scientific libraries, collecting abstracts, congress presentations and other external communications in the area of cardioverter defibrillators.

10.5.6 The inclusion and exclusion criteria.

Table B3 Selection criteria used for published studies – Outcome search

Inclusion criteria	
Population	Patients implanted with CRT-Ds
Interventions	Patients undergoing CRT-D replacement
Outcomes	Adverse events (including death); patients' quality of life and satisfaction; infection/complication rate associated with replacement
Study design	• All studies (conducted in experimental or observational setting) evaluating the risks associated with CRT-D replacement procedures (including a comparison with risks associated with de novo procedures when available) • Systematic reviews and meta-analyses analysing patients' outcomes related to CRT-D replacement procedures (including a comparison with risks associated with de novo procedures when available)

Language restrictions	English language only
Other restrictions	Full text or abstract available
Search dates	-
Exclusion criteria	
Population	Patients implanted exclusively with ICDs (i.e. ICD-VR, ICD-DR, not CRT-Ds)
Interventions	-
Outcomes	-
Study design	Editorials
Language restrictions	English language only
Other restrictions	Full text or abstract available
Search dates	-

10.5.7 The data abstraction strategy.

Tables were created with defined headings corresponding to relevant data to be extracted. Articles were manually searched for the information under each heading and this data was abstracted accordingly.

10.6 Appendix 6: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **EconLIT**

- **NHS EED.**

Pubmed was the primary database searched. Furthermore, Cochrane and ClinicalTrials.gov were searched.

10.6.2 The date on which the search was conducted.

This review was conducted on 27 May 2016.

10.6.3 The date span of the search.

In this search, no restrictions on the year of publication were applied.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Source	Search Criteria
PubMed	(longevity OR lifespan OR replacement OR drain) AND (cardioverter OR defibrillator OR icd OR crt OR resynchronization OR resynchronisation OR cardiac device*) AND (economic OR cost OR burden OR budget)
Cochrane	(longevity OR lifespan OR replacement OR drain) AND (cardioverter OR defibrillator OR icd OR crt OR resynchronization OR resynchronisation OR cardiac device) AND (economic OR cost OR burden OR budget)
ClinicalTrial.gov	
Hand-searching	Analysis of internal company documentation

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

A literature search was conducted using three main sources of clinical evidence (Pubmed, Cochrane, ClinicalTrials.gov). The evidence not indexed but included in the present submission was retrieved from an analysis of Boston Scientific libraries, collecting abstracts, congress presentations and other external communications in the area of cardioverter defibrillators.

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