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REVIEW ARTICLE

ENDURALIFE-Powered Cardiac Resynchronisation Therapy Defibrillator Devices for Treating Heart Failure: A NICE Medical Technology Guidance

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Abstract ENDURALIFE^{TM}-powered cardiac resynchronisation therapy defibrillator (CRT-D) devices were the subject of an evaluation by the National Institute for Health and Care Excellence, through its Medical Technologies Evaluation Programme, for the treatment of heart failure. Boston Scientific (manufacturer) submitted a case for the adoption of the technology, claiming that it has a longer battery life resulting in a longer time to CRT-D replacement. Other claimed benefits were fewer complications associated with replacement procedures, fewer hospital admissions, less time spent in hospital and reduced demand on cardiology device implantation rooms. The submission was critiqued by Cedar, an external assessment centre. The submitted clinical evidence showed that ENDURALIFE-powered devices implanted during the period 2008–2010 were superior, in terms of longevity, to other devices at that time. Submitted economic evidence indicated that, because of a reduction in the need for replacement procedures, ENDURALIFE-powered devices were cost saving when compared to comparator devices. Cedar highlighted uncertainty of the applicability of the clinical evidence to devices marketed today. The Medical Technologies Advisory Committee noted that this was unavoidable due to the follow-up time required to study battery life. Clinical experts noted that increased battery life is an important patient benefit. However, centres use devices from multiple manufacturers to negate pressure on clinical services in the event of a major device recall. The clinical and economic evidence showed benefits to the patient, and further analysis requested by the committee suggested that ENDURALIFE-powered CRT-Ds may save between £2120 and £5627 per patient over 15 years through a reduction in the need for replacement procedures. ENDURALIFE-powered CRT-D devices received a positive recommendation in Medical Technologies Guidance 33.

Key Points for Decision Makers

The clinical evidence submitted by the manufacturer is robust and shows superiority, in terms of longevity, of ENDURALIFE-powered CRT-D devices over other CRT-D devices implanted in the period around 2008–2010. Cost-modelling showed that longevity and price of the CRT-D device have the greatest effect on overall treatment costs. ENDURALIFE-powered CRT-D devices were shown to be cost saving compared to other CRT-D devices implanted around 2008–2010.

CRT-D device technology evolves rapidly across different manufacturers. Innovations are likely to include other components of the device and not the battery alone. It is uncertain if the evidence has direct applicability to CRT-D devices marketed today as by the time evidence is produced the devices may no longer be available.

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1 Introduction

The National Institute for Health and Care Excellence (NICE) evaluates new or innovative medical technologies through its Medical Technologies Evaluation Programme (MTEP). The programme generates guidance on diagnostic technologies and medical devices in addition to providing support for technology adoption to the National Health Service (NHS) [1].

NICE Medical Technologies Guidance (MTG) is a published completed evaluation of a new or innovative medical technology. The process has previously been described in detail [2]. Briefly, NICE publish a scope for the guidance that is followed by a submission from the technology's manufacturer. In this submission, the manufacturer will make a case for adoption of the technology and will provide both clinical and economic evidence to support their claimed benefits. The submitted evidence is reviewed and critiqued by an external assessment centre (EAC), with expertise in medical technology evaluation. The EAC presents their review and critique in an assessment report, which, in conjunction with the manufacturer's submission, is used by the Medical Technologies Advisory Committee (MTAC) during its decision process.

This paper summarises an assessment report by an EAC and shows how it was used by NICE to inform the MTG on ENDURALIFE^{TM}-powered cardiac resynchronisation therapy defibrillator (CRT-D) devices for treating heart failure. The paper is part of a series that provide an insight into the development of NICE MTG [2]. Cedar, a healthcare technology research centre formed through collaboration between Cardiff and Vale University Health Board and Cardiff University, was the EAC responsible for producing this assessment report. ENDURALIFE-powered CRT-D devices are manufactured by Boston Scientific.

2 Background to the Condition and Technology

Heart failure is a condition where an abnormality in cardiac function results in an impairment of the heart to pump blood efficiently [3]. Specifically, the condition arises from a structural or functional disorder of the heart, which impairs the ventricle's ability to fill or eject blood [4]. Heart failure can be classed as chronic or acute and can occur as a result of left ventricular systolic dysfunction (LVSD) or diastolic dysfunction where there is a preserved left ventricular ejection fraction (LVEF) [5].

Recent work combining prevalence figures with population estimates suggests that in the UK $>$ 308,000 men and 250,000 women are living with heart failure [6]. The highest prevalence of heart failure was observed in Wales and in North East England. Heart failure prevalence increased with age and was most prevalent in people aged $\geq$ 75 years.

Current NICE technology appraisal guidance recommends the use of CRT-D devices as treatment options for people with heart failure. The guidance specifically recommends CRT-Ds for use in people with heart failure who have left ventricular dysfunction and an LVEF of $\leq$ 35%, according to New York Heart Association (NYHA) class, QRS interval and presence of left bundle branch block [7].

CRT-D devices combine cardiac resynchronisation therapy, for cardiac pacing, and a defibrillator for ventricular arrhythmia treatment [7]. The CRT-D generator is combined with leads that allow sensing of the heart's electrical activity and deliver the electrical energy to the atria and ventricles of the heart. Power for the CRT-D comes from a battery which is sealed within the device itself. A CRT-D makes a small, but virtually continuous demand on battery energy for ventricular resynchronisation. In addition, where a life-threatening arrhythmia is detected by the CRT-D, a defibrillation shock delivers a large amount of energy via a capacitor to restore normal heart rhythm. Therefore, there are two distinct patterns of demand for energy placed on the battery. All CRT-D batteries deplete over time and the rate of depletion depends on factors such as the energy required for pacing, the number of shocks the CRT-D has had to deliver and whether settings such as remote monitoring are enabled. An elective replacement indicator (ERI) indicates that a limited safe quantity of battery capacity (e.g. for 3 months' operation) remains and that the whole generator must be replaced; the battery cannot be removed from the sealed CRT-D.

ENDURALIFE battery technology was designed by Boston Scientific in an effort to extend the working life of their CRT-D devices. The technology uses lithium manganese dioxide (Li/MnO_2) as its battery chemistry, which according to the manufacturer, is less susceptible to variations in voltage and resistance associated with early battery depletion. The ENDURALIFE battery has a large capacity of 2.0 Ampere-hours (Ah). In addition, the manufacturer claims that the microprocessor and circuitry of ENDURALIFE-powered CRT-Ds have been designed to use less current and that ENDURALIFE-powered CRT-Ds are both smaller and thinner than previous CRT-Ds. ENDURALIFE as a brand was launched by Boston Scientific in 2015 but the technology has been used in all their CRT-D devices since the COGNIS device in 2008. CRT-D devices are Class III medical devices under the medical devices directive and have CE mark status [8].

In their submission to NICE, the manufacturer claimed the following benefit to the patient: extended CRT-D longevity increases the interval between CRT-D

replacements. This would be beneficial for heart failure patients since CRT-D replacement is an invasive surgical procedure known to have a greater risk of complications than de novo (initial) CRT-D implant procedures.

The manufacturer claimed the following benefits to the healthcare system: a reduced chance of needing earlier CRT-D replacement will lead to savings through a reduction in hospital admissions; more efficient use of cardiology device implantation facilities as reduced replacement rates will allow new patients to be implanted within the same resource constraints, supporting the implementation of NICE's technology appraisal guidance [7], and bridging the gap with recommended levels of CRT-D implants in the UK; a reduction in costs associated with replacement such as post-operative complications and infections.

3 Decision Problem (Scope)

To focus their submission, the manufacturer must define and follow a decision problem, which is presented in a population, intervention, comparator, outcomes (PICO) table. The PICO table generated by the manufacturer was consistent with the final scope, published by NICE in May 2016 [8].

3.1 Population

In their decision problem, the manufacturer identified "patients undergoing CRT-D device implantation for heart failure" as their target population. This was in line with previously published NICE technology appraisal guidance [7].

3.2 Intervention

The scope for intervention included ENDURALIFE-powered CRT-D devices [8].

3.3 Comparator

The manufacturer identified any CRT-D that did not incorporate ENDURALIFE battery technology as a comparator [8]. Comparators were therefore typically CRT-Ds from other manufacturers.

3.4 Outcomes

The decision problem included a number of outcomes. The included outcomes were identified by the manufacturer to provide evidence for their submitted claimed benefits and included device-based, patient-related, clinical and resource use outcomes.

Device-based outcomes were relevant to all CRT-Ds and included device survival, battery survival (or time to ERI) and CRT-D component failure.

Patient outcomes included satisfaction and quality of life, while inpatient admissions and bed days (due to device-related interventions) were considered as resource use outcomes.

Clinical outcomes included device-related adverse events, number of invasive procedures (including replacement surgeries), incidence of complications (due to replacement procedures for battery depletion and/or CRT-D component failure) and death. The EAC recognised that the complication risks associated with CRT-D replacement surgery are common to any CRT-D and not just those that contain ENDURALIFE battery technology. Therefore, this evidence could be coupled with evidence on longevity or replacement rates of CRT-Ds with ENDURALIFE battery technology, in order to assess the manufacturer's claimed benefits. From a healthcare perspective, if the device was shown to have extended longevity, this could potentially reduce costs associated with hospital admissions and bed days. This would be dependent on the number of generator replacements a patient requires over their lifetime.

4 Review of Clinical Effectiveness Evidence

4.1 Manufacturer's Review of Clinical Effectiveness Evidence

The manufacturer submitted clinical evidence as outlined in the scope [8]. The manufacturer submitted a total of seven retrospective case series studies, which focused on CRT-D longevity, from six sources. Five of the included studies were available as full papers [9–13], two studies were reported as conference abstracts only [14, 15] and one study was reported in two papers at two different time-points [9, 10]; only the latest paper has been summarised (Table 1). In addition to submitting evidence on CRT-D longevity, the manufacturer also submitted a total of 19 studies to highlight the complications associated with implantable cardioverter defibrillator (ICD) and CRT-D replacement procedures, as a whole. These papers were not device or manufacturer specific. The manufacturer's submission of clinical evidence also included product performance reviews (PPRs). These reviews are produced by the five manufacturers of CRT-Ds in response to a recommendation by the US Heart Rhythm Society Task Force [16]. The PPRs aim to report device malfunctions based only on data derived from explanted devices returned to the manufacturer. Based on the status of CRT-Ds observed during follow-up and at device return, actuarial statistical methods are used to derive a cumulative survival

Table 1 Summary of evidence submitted by the manufacturer

Study reference, country, and follow-up	CRT-Ds in study	Device survival	Limitations
Alam et al. (2016) [9] USA Mean follow-up = 3.4 years (SD ±2.1); median follow-up = 3.7 years (IQR 1.6, 5.0)	ENDURALIFE-powered BSC (n = 122), non-ENDURALIFE-powered BSC (n = 51), MDT (n = 391), SJM (n = 57)	Rates of replacement due to battery depletion (ERI): BSC: 16%, MDT: 51%, SJM: 53% ($p < 0.001$)	Of 173 BSC devices studied, 122 were ENDURALIFE-powered, so comparisons by manufacturer do not have complete applicability to the scope
Ellis et al. (2016) [11] USA Mean follow-up = 3 years (SD ± 1.3)	BSC (n = 322; of which 97% were ENDURALIFE-powered), MDT (n = 794), SJM (n = 186)	Device survival and out of service reason: ERI-BSC: 0.3%, MDT: 13.5% and SJM: 3.8%	Device names were not reported in the paper itself. Proportions of devices were obtained by the manufacturer through direct contact with the authors
Landolina et al. (2015) [12] Italy Median follow-up = 43 months (IQR 18, 53)	ENDURALIFE-powered BSC (n = 291), non-ENDURALIFE-powered BSC (n = 317), MDT (n = 798), SJM (n = 172), BTK (n = 49), SOR (n = 99)	Device longevity at 5 years: BSC: 88 %, SJM: 75 %, MDT: 52%	Of 608 BSC devices studied, 291 were ENDURALIFE-powered. However, data presented on device longevity at 5 years is based on recent generation devices and all BSC devices were COGNIS devices. These are ENDURALIFE-powered
von Gunten et al. (2015) [13] The Netherlands and Switzerland Median follow-up = 4.4 years (IQR, 2, 7.3)	ENDURALIFE-powered BSC (n = 102), non-ENDURALIFE-powered BSC (n = 39), other CRT-Ds including MDT and SJM (n = 1143)	Device longevity at 5 years: BSC: 97.6%, SJM: 45.3%, MDT: 74.1%, BTK: 76.2% Device longevity at 6 years: BSC: 97.6%, SJM: 26.5%, MDT: 46.3%, BTK: 44.9%	The main paper does not state whether or not BSC devices are ENDURALIFE-powered; however, a supplementary table reports the longevity for 76 ENDURALIFE-powered COGNIS devices
Lau et al. (2015) [14] UK No mean or median follow-up stated	ENDURALIFE-powered BSC (n = 27), MDT (n = 62), SJM (n = 66)	BSC survival at 6 years: 100% Time to reach ERI for comparator devices: SJM: 2.8 years, MDT: 2.5 years	This study is only available as an abstract. Many details are not reported including patient characteristics, number of subjects per group and average follow-up
Williams and Stevenson (2014) [15] Lebanon No mean or median follow-up stated	ENDURALIFE-powered BSC (n = 51), non-ENDURALIFE-powered BSC (n = 2), MDT (n = 28), SJM (n = 10)	Devices reaching ERI at 4 years: BSC: 1.9%, SJM: 10%, MDT: 50%	This study is only available as an abstract. Many details are not reported including values for some outcome data

BSC Boston Scientific, *BTK* Biotronik, *CRT-D*(s) cardiac resynchronization therapy defibrillator(s), *ERI* elective replacement indicators, *IQR* inter-quartile range, *MDT* Medtronic, *SD* standard deviation, *SJM* St. Jude Medical, *SOR* Sorin

probability. Therefore, comparing PPRs across manufacturers may permit comparisons of CRT-D longevities. The PPRs submitted suggested that in the majority of cases the replacement of their CRT-Ds was due to battery depletion and not device malfunctions. The manufacturer also included a comprehensive description of adverse events identified in the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) and UK Medicines and Healthcare Products' Regulatory Agency (MHRA) databases. The identified adverse events highlight that CRT-Ds are Class III medical devices with indications in patients at risk of serious morbid incident or mortality, and as such can generate a large number of adverse events.

4.2 EAC Critique of Clinical Effectiveness Evidence

The manufacturer conducted two separate literature searches. One retrieved evidence for device longevity and the other retrieved evidence on the incidence of complications associated with device replacement. The manufacturer's search strategies for PubMed and Cochrane were assessed in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist [17]. The EAC considered the search strategies could be improved, and carried out its own search of the literature and adverse events, in addition to citation tracking. The EAC's literature search results were reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

methodology [18] (Fig. 1). Following its own searching, the EAC was satisfied that the manufacturer identified all the relevant literature for this technology at the time of writing their submission.

The studies on device longevity included by the manufacturer were consistent with the decision problem and the manufacturer took the reasonable step of excluding studies where ENDURALIFE-powered CRT-Ds comprised fewer than 50% of devices in the study. Participants in the included studies underwent implantation from 2008 onwards, the year that ENDURALIFE technology became available. One study included patients implanted with CRT-Ds between 1994 and 2014, but a supplement to this study separately reports the longevity of ENDURALIFE-powered COGNIS CRT-Ds [13]. There are a few limitations with the evidence submitted on device longevity. One limitation was that not all Boston Scientific CRT-Ds are powered by ENDURALIFE technology. This was further confounded by the fact not all studies have reported which CRT-Ds have been studied [11, 15]. To address this problem, the manufacturer contacted the authors and obtained the number of ENDURALIFE-powered CRT-Ds in the studies.

Of the manufacturer's submitted studies reporting complications due to replacement procedures ($n = 19$), three were systematic reviews [19–21] and included data from the majority of the primary studies submitted. The EAC selected the three systematic reviews, in addition to two primary studies [22, 23], which were not included in the systematic reviews, as evidence on complications. These studies also included data on ICD replacement. However, the EAC considered the applicability of CRT-D replacement procedures was limited only to a small extent by the inclusion of data for ICD replacement because in either case the procedure is similar.

The manufacturer submitted five PPRs in total; one for each manufacturer of CRT-Ds. PPRs have a few limitations: Boston Scientific PPRs are based on data from the US only; not all devices are returned to the manufacturer following explantation; PPR analysis assumes that a device is in service unless otherwise indicated, which could overestimate CRT-D longevity if devices that have not been returned to the manufacturer are recorded as in service instead of lost to follow-up; the definition of normal battery depletion is different for each manufacturer and means that two devices from different manufacturers that

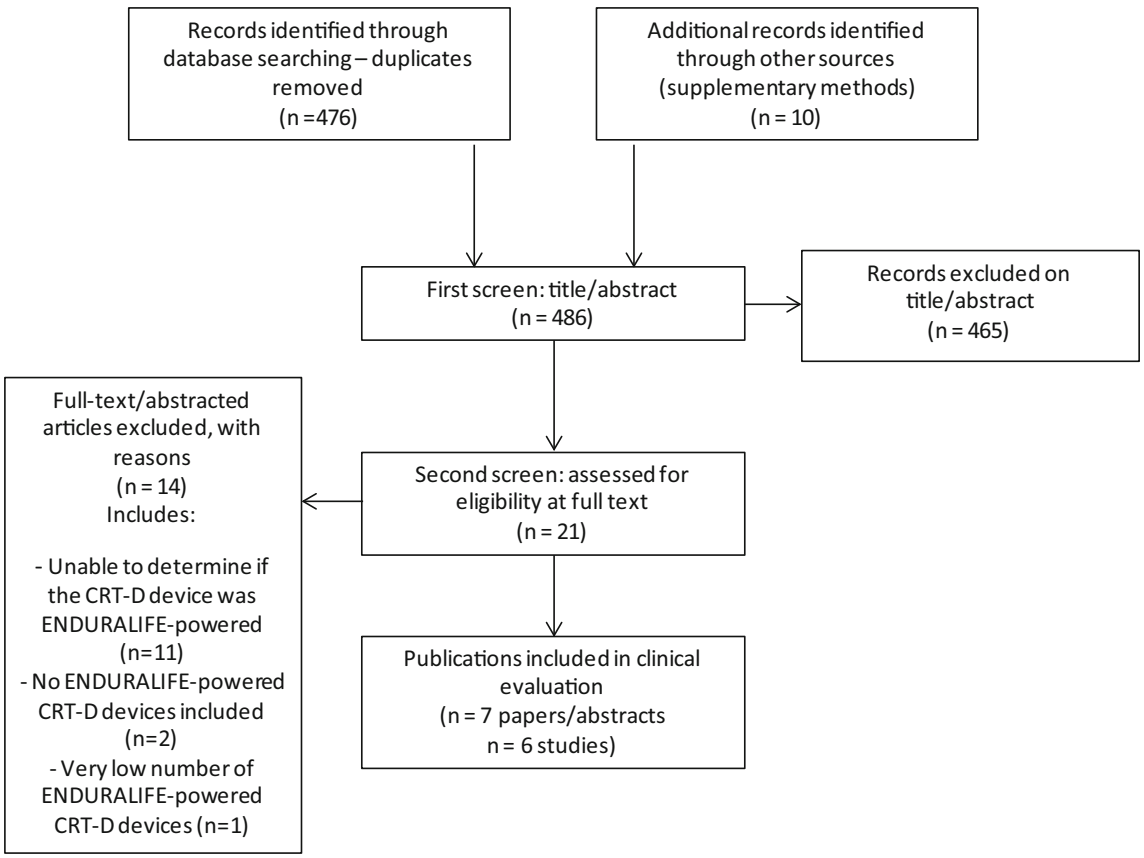

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the EAC's literature search results. *CRT-D* cardiac resynchronisation therapy defibrillator

reach a point of battery failure at the same length of follow-up may be classified as normal battery depletion or premature battery depletion (a malfunction). For these reasons, the EAC concluded that the PPRs served to indicate that ERI rather than malfunction is the most common reason for CRT-D replacement.

The manufacturer's description of adverse events related to ENDURALIFE-powered CRT-Ds, as returned from a search of the FDA MAUDE and MHRA databases, was comprehensive. The search returned > 8000 adverse events, whilst the EAC's search for adverse events in the same databases identified 2677 events. The EAC understands the manufacturer is likely to be highly vigilant for adverse events related to the implantable devices it markets and has likely identified more adverse events through its own active surveillance and close communication with regulatory bodies and clinical sites.

4.3 EAC Conclusions on the Clinical Evidence

The manufacturer's submission of published studies of CRT-D longevity provides head-to-head comparisons of ENDURALIFE-powered CRT-D devices with contemporary comparator CRT-D devices. Weaknesses in the evidence included limited applicability of some studies to the decision problem, retrospective analysis and that it is not possible to determine why study participants were implanted with a CRT-D device from a particular manufacturer.

The EAC considers that battery capacity is an important factor, which may potentially determine CRT-D device longevity, but also that it does not act in isolation and other CRT-D device components also play an important role in device longevity. Battery capacity for ENDURALIFE-powered CRT-Ds has been reported as 2.0 Ah compared with 1.0 Ah for Medtronic CRT-Ds and undisclosed for St Jude Medical CRT-Ds [12]. PPRs submitted by the manufacturer demonstrate that normal battery depletion is the main reason for CRT-D replacement, and not device malfunctions. However, due to limitations and variability across manufacturers in the methods behind PPRs, the EAC acknowledged that the published studies of longevity presented more robust data on longevity than the PPRs.

The EAC accepted the manufacturer's submission of evidence on the rate of complications following CRT-D replacement. In addition, the EAC noted that the high number of observed adverse events is likely, considering that CRT-Ds are Class III medical devices, used in people with heart failure and potential co-morbidities. However, the EAC has seen no evidence that ENDURALIFE-powered CRT-Ds present a particular risk of adverse events compared to comparator CRT-Ds.

The EAC found that the clinical evidence submitted by the company was acceptably robust and reflects the performance of ENDURALIFE-powered CRT-Ds implanted in the period 2008–2010, showing their superiority at that time in terms of longevity. However, it is uncertain whether it has direct applicability to CRT-Ds marketed today. It is likely that different manufacturers have each undertaken their own development. Such innovations are unlikely to be limited to the battery alone, but to other components of the CRT-D (e.g. capacitor, microprocessor, etc.) and how it interacts with the heart. Devices marketed today may have better longevity than their predecessors studied in the included longevity studies. Finally, whether differences in longevity between ENDURALIFE-powered CRT-Ds and comparators lead to a reduction in replacement procedures depends on patient life expectancy.

5 Economic Evidence

5.1 Manufacturer's Economic Submission

The manufacturer's economic submission included seven studies, two of which were published in full [24, 25], two full papers were academic in confidence (unpublished work) and three were conference abstracts [26–28]. All the manufacturer's selected economic studies were based outside of the UK apart from one conference abstract [28]. Therefore, the manufacturer generated a de novo economic model similar in structure to a model described in one of the unpublished papers.

Clinical model inputs on event-free battery survival were identified from an unpublished economic study, which appears to be a sub-set of the same sample reported in a previous publication [12]. Data inputs for the model on cumulative probability of patient survival were identified from another study [29]. The technology considered is the ENDURALIFE-powered CRT-D from a previously published study [12]. This study also included data on other non ENDURALIFE-powered Boston Scientific CRT-Ds in addition to comparator devices from Medtronic and St Jude Medical. Data on complications associated with replacement procedures were identified from a study submitted as part of the manufacturer's clinical evidence [19].

The de novo model was a decision tree with a 6-year time horizon from an NHS perspective with ENDURALIFE-powered CRT-Ds as the intervention and CRT-Ds manufactured by Medtronic and St Jude Medical as comparators. For each CRT-D manufacturer there is a branch for complications or no complications. Both these cases have further branches for death, replacement or no replacement at 1 year and at each subsequent year. Key assumptions of the model include: all device capital costs

are equal; all manufacturer warranties are equal; patients attend 6-monthly outpatient follow-up appointments with an additional post-procedure appointment; data from published literature on devices implanted between 2008 and 2010 can be applied to the latest generation devices currently available from the same manufacturers.

To factor in improvements over time of comparator CRT-Ds, an estimated percentage improvement in projected battery survival was applied to Medtronic CRT-Ds only. The manufacturer's base case showed that Boston Scientific ENDURALIFE-powered, St. Jude Medical and Medtronic CRT-Ds cost £22,322, £27,309 and £29,158, respectively per patient over 6 years. The manufacturer therefore estimated that using an ENDURALIFE-powered CRT-D would save £4986 and £6836 per patient over a 6-year period when used in place of a Medtronic or St Jude Medical CRT-D, respectively.

5.2 Critique of Economic Evidence

The manufacturer's literature search was limited to three publicly available databases and therefore did not include all the databases specified by NICE in its submission template. Search terms used by the manufacturer were somewhat limited. Therefore, the EAC conducted its own search using the recommended databases and more comprehensive search terms. Following its own literature search, the EAC was satisfied that the manufacturer's search results were reasonable. The population used by the manufacturer in its selection of economic evidence differed from the population specified in the decision problem. The EAC acknowledged that the manufacturer's broader population definition is likely to be as a result of a lack of detail in the published evidence on the specific criteria used to define heart failure and CRT-D use from the relevant NICE technology appraisal guidance [7]. The EAC excluded three papers that had been included by the manufacturer [24–26] as they were outside of scope [8]. The manufacturer described the included economic studies and carried out a quality assessment of each. Finally, due to the rapidly evolving technology the published economic evidence relates to devices no longer marketed.

5.3 Critique of the De Novo Model

The manufacturer did not approach clinical advisers to assess the applicability of clinical or resource inputs used in the model. They performed internal and external quality assurance to ensure the model performs as intended. The manufacturer conducted a one-way sensitivity analysis to identify thresholds where the model becomes cost-neutral. Their analysis explored differences in device survival and device cost.

The 6-year time horizon was a limitation of the model and potentially exaggerates the cost saving of a slightly longer-lasting device. The EAC considered that it is unclear whether a small difference in CRT-D longevity across suppliers would result in a fewer total number of replacement procedures over the entire lifetime of a patient, but was unable to identify a reliable study of patient life expectancy in the CRT-D-implanted population. For this reason, the EAC obtained patient survival data from the National Institute for Cardiovascular Outcomes Research (NICOR) following expert advice and replaced the data used by the manufacturer [29]. ENDURALIFE-powered CRT-Ds remained cost saving when using the manufacturer's base-case device cost. At the lowest and highest list prices, for each of the three manufacturers, ENDURALIFE-powered CRT-Ds become more expensive than those from Medtronic; however, they remain cost saving compared with those from St Jude Medical. The MTAC judged that the 6-year time horizon gave rise to uncertainty surrounding the cost case. Data on patient survival was obtained from NICOR and the EAC carried out extrapolation of CRT-D lifespan to 15 years. Using the extrapolated data and the manufacturer's base-case average selling price, the EAC calculated ENDURALIFE-powered CRT-Ds cost £28,234 compared with £30,354 and £33,861 per patient over 15 years for St Jude Medical and Medtronic CRT-Ds, respectively, and could save between £2120 and £5627 per patient over 15 years in patients aged 50–84 years.

The company based the costs of technologies on the assumption that all the devices cost the same. In the model, the device cost is a key driver and therefore this was a significant weakness of the model. The EAC obtained list prices from Boston Scientific, St. Jude Medical and Medtronic and carried out threshold analysis allowing price differences between the devices and calculated the threshold at which the intervention becomes cost saving compared to the comparators. The results showed that, accepting all else in the model, ENDURALIFE-powered CRT-Ds remain cost saving until they are £4858 and £3858 more expensive to purchase than Medtronic and St Jude Medical CRT-Ds, respectively.

The EAC sought expert clinical advice on rates of complications associated with replacement procedures and included a Danish cohort study, which provided the necessary data, based on the recommendation of the expert advice [30]. The EAC considered that the manufacturer's sensitivity analysis covered the range of different complications reported in the cohort study apart from rate of infection. The EAC included the rate of infections from the cohort study in the model and the effect was negligible.

The EAC also obtained information on warranties from the manufacturers and carried out analysis based on this.

ENDURALIFE-powered CRT-Ds remained cost saving. The EAC also substituted the payment by results (PbR) tariff, used by the manufacturer for procedure costs, with NHS reference costs from 2014–2015. This increased the cost of ENDURALIFE-powered CRT-Ds from £22,322 in the base case to £30,957. This was still cost saving compared to Medtronic and St Jude Medical CRT-Ds (£37,087 and £35,429, respectively) but was less so than in the manufacturer's base case.

6 NICE Guidance

6.1 Provisional Recommendations and Consultation

In September 2016, MTAC convened to make provisional MTG recommendations on ENDURALIFE-powered CRT-D devices, with the assistance of the EAC, two clinical expert advisors, and a patient representative. The committee considered that ENDURALIFE-powered CRT-Ds have a greater battery capacity and longer battery life compared with other CRT-Ds available at the time of the published studies. It noted that, because of the follow-up time needed to study battery life, the retrospective, observational studies presented included CRT-Ds that were no longer marketed. In the absence of data on currently marketed devices, the committee was advised by experts that the company's claims relating to battery life and the ENDURALIFE battery technology have been borne out in their own subsequent clinical experience, as well as in the published literature. The committee was advised that replacement procedures are associated with a risk of serious complications and that complications are more common in replacement than primary implants. Infection can have major consequences in terms of patient morbidity and resource use, including the need for hospital admission that may last days or weeks. The committee heard from a patient expert that replacement procedures have a detrimental impact on quality of life.

The committee further discussed issues concerning NHS resources and costs. Battery depletion accounts for 80–90% of CRT-D replacements. The committee heard from experts that, despite increased battery life being an important patient benefit, it is standard practice for a single centre to use CRT-Ds from more than one manufacturer. The rationale is to spread the risk of undue pressure on clinical services in the face of possible future device-related technical failure necessitating recall and replacement. In view of this important consideration, professional advice was that it was unwise for a department to rely entirely on the use of a CRT-D from a single manufacturer.

Regarding costs, the committee was advised that the average selling prices used in the company's base case was a better reflection of what the NHS pays for CRT-Ds; furthermore, the committee concluded that it would be difficult to ascertain actual NHS prices for ENDURALIFE-powered and comparator CRT-Ds. Overall, the committee concluded that using ENDURALIFE-powered CRT-Ds in patients with heart failure is likely to cut costs by reducing the number of replacement procedures.

Following the meeting, draft guidance was produced which was released for public consultation between 26th October and 23rd November 2016. In total, 58 comments were submitted by external stakeholders. These were individually addressed during the MTAC meeting held on 16th December 2016. The comments related to recommendations based on evidence on devices no longer in use, suitability of a single technology assessment, factors other than battery capacity affect battery longevity, cost modelling and matters of fact or lack of clarity in the draft guidance. Some of the comments resulted in minor amendments to the guidance to further clarify the committee's considerations.

6.2 Final NICE Guidance

In December 2016, NICE made the following recommendations concerning the use of ENDURALIFE-powered CRT-D devices for treating heart failure:

1.1 The case for adopting ENDURALIFE-powered CRT-D devices for treating heart failure is supported by the published evidence. Extended battery life is of clinical and patient benefit and associated with fewer replacement procedures.

1.2 ENDURALIFE-powered CRT-Ds should be considered as an option in people offered CRT-D devices in line with NICE technology appraisal guidance on ICDs and cardiac resynchronisation therapy.

1.3 Cost modelling was based on published data using predecessor devices, and showed that the price and lifespan of the CRT-D have the greatest effect on overall treatment costs. Assuming an average selling price of £12,404 across different devices, using ENDURALIFE-powered CRT-Ds may save between £2120 and £5627 per patient over 15 years through a reduction in the need for replacement procedures. This could save the NHS in England around £6 million in the first 5 years.

Following the resolution stage, it was concluded that recommendation 1.3 contained points that required clarification through minor revisions which did not affect the Committee's recommendations [31].

7 Key Challenges and Learning Points

The key challenge faced by the EAC and the MTAC was the applicability of the available evidence to CRT-D devices on the market today. The evidence presented for

CRT-D longevity was for devices implanted in around 2008–2010. Many of these devices are no longer marketed. In addition, it is likely that there have been numerous innovations across different manufacturers and that these innovations are unlikely to be limited to the battery alone.

The manufacturer's de novo economic model had some limitations and weaknesses. The EAC liaised with clinical experts to decide which study should be used to obtain data on rates of complications associated with CRT-D device replacement procedures. In addition, the EAC obtained list prices for ENDURALIFE-powered and comparator CRT-D devices, obtained warranty data from comparator manufacturers and NHS reference costs. All the extra information obtained by the EAC was substituted into the formulae in the model and threshold analysis, using the average selling price of ENDURALIFE-powered CRT-D devices, and sensitivity analysis for complication rates was carried out by the EAC.

The MTAC considered that the 6-year time horizon made the cost case uncertain and asked the EAC to carry out further work. The EAC extrapolated CRT-D lifespan to 15 years using a survival profile for comparator devices. In addition, the EAC contacted NICOR to obtain unpublished data in confidence on patient survival for patients aged 50–84 years at primary implantation. Using these data, the EAC extrapolated patient survival to 15 years.

Evidence submitted for this MTG included CRT-D devices that are no longer marketed. However, it was noted by MTAC that this was unavoidable owing to the follow-up time required to study battery life. The MTAC was advised by clinical experts that published, peer-reviewed clinical studies are a more reliable source of information than unpublished, extrapolated and predicted lifespan data.

8 Conclusion

ENDURALIFE-powered CRT-Ds received a positive recommendation from NICE and should be considered as an option for people requiring CRT-D devices in line with previous NICE technology appraisal guidance [7]. Published evidence showed superiority of ENDURALIFE-powered CRT-Ds implanted in the period 2008–2010 in terms of longevity. The EAC highlighted its uncertainty of the applicability of the evidence to CRT-D devices marketed today. However, the MTAC noted this was unavoidable due to the follow-up time required to study battery life. In addition, the EAC noted whether differences in longevity between ENDURALIFE-powered CRT-Ds and comparators lead to a reduction in replacement procedures depends on patient life expectancy. ENDURALIFE-powered CRT-Ds were shown to be cost saving when compared to comparator CRT-Ds through a reduction in the need for replacement procedures. Clinical experts informed MTAC that increased battery life is an important patient benefit. However, in practice the risk of pressure on clinical services, due to possible future device-related technical failure leading to recall and subsequent replacement, is reduced by using CRT-Ds from more than one manufacturer.

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Compliance with Ethical Standards

Conflict of interest Cedar is funded by the NICE Medical Technologies Evaluation Programme to act as an EAC for the Medical Technologies Evaluation Programme. AC and GCR are NHS employees, and the NHS has a financial interest in the guidance on which this project is based. LM is a NICE employee and had no role in the production of the EAC assessment report but contributed to the preparation of this manuscript. JE and HM declare no conflicts of interest. This summary of Medical Technology Guidance was produced following the publication of the final guidance report. The article has not been externally peer reviewed by Applied Health Economics and Health Policy.

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