NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

MTG review decision document

Review of MTG33: ENDURALIFE powered CRT-D devices for treating heart failure

This guidance was issued in March 2017.

NICE proposes an amendment of published guidance if there are no changes to the technology, clinical environment or evidence base which are likely to result in a change to the recommendations. However, the recommendations may need revision to correct any inaccuracies, usually in relation to providing a more accurate estimate of the results of the cost modelling. The decision to consult on an amendment of published guidance depends on the impact of the proposed amendments and on NICE's perception of their likely acceptance with stakeholders. NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance.

1. Recommendation

Amend the guidance to reflect the new costs for ENDURALIFE.

Please see Appendix 1 for a list of the options and their explanations for consideration.

2. Original objective of guidance

To assess the case for adoption of ENDURALIFE-powered CRT-D devices for treating heart failure.

3. Current guidance

1.1 The case for adopting ENDURALIFE-powered cardiac resynchronisation therapy-defibrillator (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 implantable cardioverter defibrillators 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 £2,120 and £5,627 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.

4. Rationale

The original guidance recommended the use of ENDURALIFE-powered CRT-D devices for treating heart failure. In total, 14 new studies were identified that are in line with the evidence presented in MTG33. For the cost case, the company requested to use average selling prices and inflate these and procedural complications, procedure and follow up costs to 2020 prices. The technology remains cost saving.

5. New evidence

The search strategy from the original assessment report was re-run. References from May 2016 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5.1 Technology availability and changes

The technology is still available to the NHS in the UK. No new models of the technology have been launched since the original guidance was published. The CE mark, indication and costs remain unchanged considering inflation to 2020 prices.

5.2 Clinical practice

The NICE pathway is chronic heart failure in adults: management

NICE's guideline has been updated and replaced since the publication of ENDURALIFE guidance by chronic heart failure in adults: diagnosis and management in September 2018. There are no changes in the recommendations. CRT-Ds are recommended as an adjunctive treatment option for heart failure in people on optimal medical therapy who have left ventricular dysfunction with a left ventricular ejection fraction of 35% or less.

All 4 clinical experts contacted during guidance review said that there have been no substantial changes to the clinical pathway.

5.3 NICE facilitated research

None.

5.4 New studies

The updated literature searches identified 14 studies on the use of ENDURALIFE published since MTG33. Nine published studies were included for adverse events associated with CRT-D replacement. Four published non-clinical studies and 1 economic study were included for projected battery survival. The study design, population and results of these studies are summarised below.

Adverse events associated with CRT-D replacement

Systematic review

McCarthy et al. (2020) is a systematic review that included 37 studies, 2 RCTs, 5 prospective and 30 retrospective cohort studies. In total, 238,949 patients needing generator replacement of previously implanted ICD/CRT-D devices. The overall median rate of infection was 2.01% (range 0.03% to 9.27%; n=2-8.078), the median rate of lead malfunction or lead dislodgement was 1.88% (range 0.06% to 9.42%; n=78,892) and the median incidence of hematoma occurrence was 1.22% (range 0.17% to 2.53%; n=80,268). The median reported rate of surgical reintervention was 4.57% (range 0.38% to 10.31%; n=1,745), and median procedure-related mortality was 0.04% (range 0% to 0.1%; n=78,195). The median rate of inappropriate ICD therapy after generator replacement was 4.7% (range 0 to 10.6%; n=1,630) with an annualised event rate of 1.88%. The median rate of appropriate ICD

therapy after generator replacement was 23.03% (range 10.9 to 31.4%; n=5,938) with an annualised event rate of 8.52%.

Observational studies

Zacà et al. (2020) and Biffi et al. (2019) both report on a prospective, single-arm, multicentre cohort study in Italy. A total of 983 patients of which 454 patients underwent CRT-D replacement and 83 patients underwent an upgrade from ICD to CRT-D. A total of 104 adverse events (AEs) occurred and the overall rate of AEs associated with ICD replacement/upgrade was 10.9 events per 100 years. Incidence and rate of AEs was 13.2 events per 100 years for CRT-Ds. Cardiac implantable electronic device-related AEs occurred in 3.3 events per 100 years, bleeding AEs in 3.4 events per 100 years, and infection AEs in 1.6 events per 100 years. Predictors of AEs were hospitalisation in the month prior to the procedure (HR 2.23) and upgrade procedures (HR 1.75). In total, 220 patients were hospitalised and 7% died. Predictors for heart failure hospitalisations were atrial fibrillation (HR 1.77), chronic kidney disease (HR 2.36) and all cause hospitalisation within 30 days prior to procedure (HR 5.61). The mean cost per heart failure hospitalisation was €5662 ± 9497, while the mean cost per patient was €9369 ± 12 687.

Feng et al. (2019) is a retrospective database review study in China. Patients with cardiac implantable electronic device implantation (n=4,959) from 2001 to 2016 were included. The overall rate of infection was 0.56% (n=28) of which 15 were during a replacement procedure and 13 were during a primary procedure. Predictors of infection included gender, age, replacement and use of antibiotics.

Looi et al. (2019) is a retrospective observational study in Northern New Zealand. 61 of the 385 patients with heart failure implanted with primary prevention ICD or CRT-D underwent generator replacement. Of these, 36.1% were CRT-Ds and mean longevity was 5.5 ± 1.6 years. There were 6 (9.8%) procedure-related complications. The 1, 3 and 5-year mortality risk was 5.2%, 8.2% and 18.4%, respectively. This study was included in the systematic review by McCarthy et al. (2020).

Yang et al. (2019) is a retrospective analysis of the Korean HIRA database. Infection rate for all CRT-P & CRT-D patients (n=698) was 2.26 per 100 person years, for first implantation (n=555) 1.46 per 100 person years, and for replacement 6.77 per 100 person years. The average cost of infection hospital admission per person with CRT-P or CRT-D was $29,674 ± 9,012. The most important risk factor for infection was generator replacement, suggesting generator

replacement should be performed cautiously to avoid cardiac implantable electrical device infection.

Clementy et al. (2018) is a retrospective analysis of the French National Hospital Database. A total of 78,267 patients with de novo cardiac implantable electronic device implantation or replacement interventions, of which 4,078 were CRT-D patients. The one-year infection rate for de novo CRT-D implantation was 1.1% and 2.5% for CRT-D replacement devices. The three-year infection rate for de novo CRT-D implantation was 1.6% and 3.9% for CRT-D replacement devices. Mean 12-month infection related costs were €24,643 for de novo CRT-D implantation and €27,649 for replacement CRT-D.

Ludwig et al. (2017) is a retrospective analysis of German health claims data. A total of 4,699 patients with an initial ICD/CRT-D implant or replacement during 2009 to 2013. There were 158 cardiac device infections (CDIs) in the 12 months after implantation, 2.9% for de novo and 4.4% for replacements ($p<0.01$). Mean 3-year incremental expenditure per patient for patients with CDI compared with controls was €31,493 for de novo implant patients and €33,777 for replacement patients.

Weng et al. (2017) is a retrospective cohort analysis of 173 patients in Canada implanted for primary prevention subsequently undergoing ICD (n=66) or CRT-D (n=107) generator replacement. Reasons for replacement included battery depletion (63.7%), upgrade (19%), battery lead and upgrade (11.2%), device infection (1.7%), erosion (1.1%) and device advisory (2.2%). Patients with no ongoing theoretical indication had lower mortality (HR 0.39, p=0.0495), appropriate shock rate (HR 0.29, p=0.04) and appropriate ICD therapy (HR 0.30, p=0.012) compared to patients with ongoing theoretical indication. This study was included in the systematic review by McCarthy et al. (2020).

Technical assessment – battery longevity

A technical report was commissioned during the original guidance development that included simulated bench testing of Enduralife because of the lack of long-term clinical data. [redacted] No inferences were drawn for devices produced by other manufacturers as tests and calculations are not standardised. Four published non-clinical studies provide additional comparative evidence on projected battery longevity.

Houser et al. (2021) is a comparative study based on manufacturers product performance reports from 2019. It includes CRT-Ds, market

released in the USA from 2010-2019, from Boston Scientific (n=100,617), Medtronic (n=186,453), Abbott (n=192,510) and Biotronik (n=13,898). The results showed that most of the malfunctions occurred in Abbott devices, followed by Boston Scientific and Medtronic. Furthermore, Boston Scientific CRT-D devices showed significantly longer battery survival compared with Abbott, Medtronic and Biotronik ($p<0.001$).

Paton et al. (2020) is a comparative study based on reported battery capacities and projected longevities for standardised settings stipulated by the French Haute Autorite´ de Sante (HAS). For Boston Scientific, the CRT-D Resonate X4 device was used. The manufacturer projected longevity based on the most basic settings showed that Boston Scientific had the longest battery life (14.7 years) compared with Microport (11.7 years), Abbott (11.1 years), Biotronik (10.1 years) and Medtronic (5.8 years). When using the HAS requirements, declared battery longevity was equal for Boston Scientific and Microport (8.3 years), followed by Abbott, Medtronic and Biotronik (7.3, 7 and 5.5 years, respectively).

Lau (2019) is a comparative study based on projected longevities, calculated to standardised settings across manufacturers. One CRT-D device was included for each company. The results showed that Microport (13.1 years; range 8.5 to 12.6 years) had the best (predicted) battery longevity, followed by Boston Scientific (11.6 years; range 8.4 to 11.5 years), Abbott (8.4 years; range 5.8 to 8.5 years), Biotronik (7.8 years; range 5.5 to 8 years) and Medtronic (7 years; range 4.7 to 7.1 years).

Manuwar et al. (2018) is a comparative study based on manufacturers' predicted longevities. CRT-Ds were set at 15% A and 100% biventricular (Bi-V) pacing with zero clinical shocks. The longevity comparisons were included a single model per manufacturer. Predicted battery longevity was highest for MicroPort (12.1 years) followed by Boston Scientific (9.4 years; Autogen EL and X4), Abbott (8.4 years), Biotronik (7.5 years) and Medtronic (6.8 years).

Economic modelling study

Schmier et al. (2017) is an economic simulation study using a Monte Carlo Markov model. Patients implanted with ICDs and CRT-Ds were included. The results showed that as battery longevity increases, patients experienced fewer adverse outcomes and healthcare costs were reduced. An increase in battery longevity in CRT-Ds yielded reductions in numbers of revisions (by 23%), battery changes (by 32%), infections (by 22%), non-infectious complications (by 8%) and

total costs per patient (by 10%). Patients receiving CRT-Ds with an extended battery had total costs reduced by about $5,981 per patient.

5.5 Cost update

Updating the original MTG33 model using the manufacturer's preferred cost update strategy (NHS Tariff costs and Bank of England inflation rates) results in a potential saving of £2,614 to £6,941 per patient over 15 years through a reduction in the need for replacement procedures when ENDURALIFE-powered devices are used compared to competitor devices. Using NHS Reference Costs (and Bank of England inflation rates), these potential savings range from £2,313 to £6,140. The full costing report can be found in Appendix 3.

6. Summary of new information and implications for review

The new evidence is unlikely to have a material effect on the recommendations in the published guidance. The new published evidence supports the committee's clinical conclusions from the original guidance. It showed that replacing CRT-D devices have a higher risk of complications than de novo procedures. It also showed that in 2 out of the 4 studies, ENDURALIFE-powered CRT-Ds have longer projected battery survival. In the other 2 studies, Microport showed the best battery longevity followed by ENDURALIFE-powered CRT-Ds. A costing update was done by the EAC which showed that ENDURALIFE-powered CRT-Ds are still cost saving.

There were no reports on the MHRA website for ENDURALIFE-powered devices. However, the FDA MAUDE website listed 8,758 reports from May 2016 to January 2021. Most of these were reporting malfunctions and defects of the device with no morbidity. In total 89 deaths (1%) were reported of which 36 (0.4%) were not related to the device.

7. Implementation

According to the company ENDURALIFE-powered CRT-D devices have been used by all major NHS hospitals implanting CRT-D devices.

8. Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were raised in the original guidance. No new equality issues were identified during guidance review.

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Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	Yes
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

Chronic heart failure in adults: diagnosis and management (2018) NICE guideline NG106

Acute heart failure: diagnosis and management (2014) NICE guideline CG187

COVID-19 rapid guideline: acute myocardial injury (2020) NICE guideline NG171

In progress

Permanent His-bundle pacemaker implantation for heart failure. NICE interventional procedure. Publication expected April 2021

Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure. NICE interventional procedure. Publication date TBC

Registered and unpublished trials

Trial name and registration number	Details
LONGEVITY Study. Evaluation of the Device and Battery Longevity of Boston Scientific Market-released ICD and CRT-D Devices ClinicalTrials.gov Identifier: NCT02091011	It is a prospective cohort study to determine the rate and cause of device replacements at 5 years post-implantation. It will assess the battery and device longevity of the Implantable Cardioverter Defibrillators (ICD) and CRT-D Cardiac Resynchronization Therapy Defibrillator (CRT-D) devices. Status: active, not recruiting. Actual enrolment: 1600 participants Devices: Boston Scientific ICDs and CRT-Ds. Estimated completion date: June 2021. Country: 80 study locations (US, Canada, Europe, Japan, Korea). This study was reported as an ongoing study in section 5.1 in the original

Appendix 3 – EAC costing report

Costing update report of MTG33: ENDURALIFE powered CRT-D devices for treating heart failure

This medical technology guidance was published in March 2017.

All medical technology guidance is reviewed 3 years after publication according to the process described in the MTEP Interim addendum on guidance reviews.

This report is part of the information considered in the guidance review. It describes an update of the cost model so that it reflects any new relevant information including revising the cost and resource parameters to current values. The results from the updated cost model are used to estimate the current savings associated with the use of the technology.

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1. Background

The manufacturer (Boston Scientific) supplied a decision tree cost model which compared Boston Scientific CRT-D implants (using the ENDURALIFE battery) against Medtronic and St Jude (now sold as Abbott) devices. Each initial implantation could incur complications or no complications. At the end of each year

the outcomes were death, no replacement, replacement with complications, or replacement without complications. Device costs were equal and the time horizon was 6 years.

Patient survival post-implant was based on a published economic analysis (Yao et al 2007) from the CARE-HF study (Cleland et al 2005). This used cardiac resynchronisation implants without defibrillator functions, with a mean follow-up of 2.45 years.

Battery longevity was based on an economic analysis (unpublished at the time; Landoliona et al 2017) of an observational study (Landolina et al 2015). The economic paper used 6 years of follow-up data on devices from Boston Scientific (with ENDURALIFE), Medtronic and St Jude Medical, implanted between 2008-2010. The manufacturer's model was based on data from 'recent-generation' devices, available since 2007. Landolina et al (2017) does not report whether their analysis includes multiple device replacements or only the first replacement.

The procedure complication data was taken from Tang et al (2010). Clinical costs were taken from the NHS payment-by-results tariff.

Key assumptions in the manufacturer's base case model are:

- The cost of the device is the same as the cost of the comparators.
- The warranty for the comparators is the same as for Boston Scientific devices.
- Patients attend 1 post-procedure appointment plus follow-ups every 6 months.
- Cost of warranty is not explicit in the model and therefore is assumed to be included in the cost of the device and equal for all devices.
- Data on devices implanted between 2008 and 2010 are still appropriate.

The manufacturer's base case reported that ENDURALIFE devices were £6,836 cheaper than Medtronic devices and £4,986 cheaper than St Jude devices over 6 years.

The EAC conducted substantial additional modelling for the Assessment Report, including altering device costs, using NHS Reference Costs instead of tariff, and changing complication rates. The guidance (MTG33; NICE 2017) notes that the device costs are a main driver in the economic model, whereas infection rates and warranties exerted little effect on the cost rankings. They also noted that the 6-year time horizon was a cause of uncertainty that could affect the cost-effectiveness of the technology.

Further modelling was conducted using patient survival data from NICOR (National Institute of Cardiovascular Outcomes Research) in patients aged 50-85 years at implant. This and battery longevity were extrapolated to 15 years. The company's

model could not be extended in this way, so the EAC created a new version of the model using a 15-year time horizon alongside the manufacturer's original model structure and inputs. The result was that ENDURALIFE could save between £2,120 and £5,627 per patient compared to standard battery devices. These are the cost savings referred to in the recommendations of MTG33, not those produced using the manufacturer's model. There were continuing concerns about whether recent developments in competitor batteries would obviate the longevity advantage of ENDURALIFE.

The objectives of this report are to:

- Confirm whether the assumptions used in the original model are still valid
- Obtain current prices for the technology, comparators and resource use

2. Current validity of model

The experts agreed that there were no substantial changes to the clinical pathway guidelines. One expert has noted the development of His Bundle pacing and that this might affect lead placement and consequently device selection.

Nevertheless, experts have highlighted that some of the assumptions made in the original report might not hold true and hence affect the validity of the model.

1. Three experts have indicated considerable variability in device costs. Three have indicated that their Trusts purchase the devices via national contracts, while one indicated that their Trust negotiates their own contracts. Devices can be purchased as systems for de novo implantation or as generators for replacement; the system price is more expensive as it contains additional components. CRT-D devices are listed as 'high cost tariff excluded devices' (HCTED) by NHS Improvement and, as such, they are paid for separately to the tariff for the procedure. This contract is now managed nationally by NHS Supply Chain, whereas it was managed locally prior to 2016 (the time of MTG33). The EAC has confirmed that there is a substantial variation in NHS prices for CRT-D generators from five manufacturers via NHS Supply Chain. Variation exists between manufacturers and between products within manufacturers. The presence of NHS Supply Chain prices raises the question whether the assumption of using the same price ENDURALIFE devices and competitor devices is valid. NHS Supply Chain prices can be used to 'sense-check' the inflation uplift to the previous selling prices.
2. In the opinion of four experts, the cost of the CRT-D device's warranty is included in the product price. Two experts have stated that the warranty varies between manufacturers and two stated that it is similar between the

manufacturers. The EAC does not believe this assumption to be crucial for the overall validity of the model as the original report noted that warranties on these devices are rarely claimed and that altering these inputs had little effect on the overall costs.

3. It can no longer be assumed that patients attend 6-monthly outpatients' appointments. Many are seen remotely and even if seen face-to-face the frequency can vary from 6 to 12 months. This is both centre and patient dependent. Experts highlighted that follow-up on the device and on the patient are different events. It also cannot be assumed that the follow-up is carried out by a medical consultant, with two experts indicating that these are usually physiologist led appointments. Additionally, the move to remote appointments may be a temporary measure related to Covid procedures. Nevertheless, patient follow-up does not vary between devices (unless there is a device specific safety alert) and as such will not impact differential cost savings.

4. The four experts do not think that data from published literature on devices implanted between 2008 and 2010 can be applied to current products. Experts have highlighted a variety of changes to both battery technology and other features of CRT-Ds that affect battery life. These have been implemented by multiple CRT-D manufacturers. Microport and Biotronik are both now using Li/MnO_2 battery chemistry in their devices (similar to ENDURALIFE), while others have increased the capacity of their Li/SVO-CFx chemistry systems. Boriani et al (2018) note a general increase in battery capacity and changes in battery chemistry between 2006 and 2017. Changes in other aspects of device hardware and software can also contribute to battery life by making devices more efficient. The manufacturer acknowledged general improvements in battery life over time in their original submission; they extended the battery life of Medtronic products by 17% over 6 years in their sensitivity analysis. So, it is uncertain whether current ENDURALIFE devices have a longer battery life than competitors. Some of the device models used in the original economic model appear to be unavailable. Also, Lau (2019) did not find that ENDURALIFE powered devices offered the longest longevity, though it was based on mathematical modelling rather than real-life patient data, and pulse width was not kept constant between all the devices used in the analysis. In the absence of additional data, we conclude that battery life assumptions used in the MTG33 guidance are no longer appropriate.

5. The original cost model compared ENDURALIFE Boston Scientific Devices with Medtronic and St Jude (now sold as Abbott) devices. While all experts have indicated that they use Medtronic products frequently, there is variability in the use of products from the other four major manufacturers, including

Boston Scientific. The EAC believes that to be representative of nation-wide practice, the analysis should compare devices from all five manufacturers.

Based on expert advice, the EAC considers that some of the assumptions from the original model are no longer valid. The substantial uncertainties around devices costs and battery longevity suggest that a simple cost update is not appropriate.

3. Updated input parameters

The EAC has considered the cost update information provided by the manufacturer, the information provided by the clinical experts, as well as information available from NHS Tariff and NHS Reference Costs for updating the model parameters. The EAC decided to analyse two scenarios: one using the 2020-2021 NHS Tariff values (NHS England and NHS Improvement, 2020) and one using the 2018-2019 NHS reference costs (NHS England 2020), in both cases these were the most up-to-date values available.

Patient follow-up frequency has not been updated. This frequency is variable between patients and centres, but is not affected by what device the patient receives. It also has little effect on the model results, as such these inputs were not altered (Table 1). The cost has been updated using a 'consultant led single professional' follow-up value (WF01A for TFC 320). This is £78 (same as submitted by the manufacturer) on the NHS Tariff and £135 (NHS England and NHS Improvement, 2020) on NHS Reference Costs (NHS England 2020). Two clinical experts noted that not all follow-ups are done by a medical consultant.

The experts suggested various complication rates. One expert referred to a Danish study by Kirkfeldt et al (2014) referenced in the original assessment report. For de novo procedures experts stated infection rates ranging from 0.6% to 1.3%, while complication rates ranged from 6% to 6.7%; for replacement procedures the ranges were 1.3% to 1.5% and 3.5 to 9.6% respectively. One expert stated an overall infection rate of 1% in their recent practice, with all cases attributed to replacement procedures, but highlighted that this might have been affected by other factors and does not feel confident in the representativeness of these figures without carrying out a full departmental audit. Considering the lack of agreement between the experts, the EAC decided to use the same rates for all complications as have been used in the original report (Table 1).

Table 1: Input Parameters For 2020 (unchanged from MTG33)

Parameter		**Value**
Follow-up	Post procedure	1
	Routine	2

Complication - De Novo	Infection	2.40%
	Complication	8.50%
	Pocket	0.50%
Complication - Replacement	Infection	2.40%
	Complication	8.50%
	Pocket	0.50%
Warranties		0.00%
Discount Rate		3.50%

The EAC has adjusted the original complication costs using the Bank of England's inflation calculator, as used in MTG33 (Bank of England, 2021). Nevertheless, we consider that it would be more appropriate to use Personal Social Services Research Unit's NHS Cost Inflation Index (NHCII). The manufacturer has suggested the following costs of infection, complication requiring intervention, and device-pocket problems requiring intervention: £24,708, £6,981 and £20,436 respectively (Table 2). The value for general complications is taken as the cost of lead displacement, and the pocket related problem value is an implantation cost. These costs were obtained by inputting the values used in TA314 (Colquitt et al 2014) as true in 2014, then inflating to 2020. However, Colquitt et al (2014) obtained their costs through a combination of values from the 2012-2013 NHS Tariff and 2010-2011 NHS Reference Costs.

The EAC noted that inflating these 2014 prices to 2015 does not result in the values used in the manufacturer's submission in 2016. The EAC has therefore inflated the values used in MTG33 to 2020 values (Table 2).

Table 2: Complication Cost Inflation Comparison

Colquitt et al (2014) labels		*Infection*	*Lead displacement*	*Implantation cost*
Source	**Year of costs**	**Infection**	**Complication**	**Pocket**
Colquitt et al 2014	Uncertain	£21,580	£6,097	£17,849
MTG33	2016	£21,774	£6,152	£18,010

Manufacturer	2020	£24,708	£6,981	£20,436
EAC	2020	£24,686	£6,975	£20,418

Despite misgivings about the use of average device costs and the chosen inflation index the EAC has continued with this methodology. We have though identified a problem with the manufacturer's original submission. They inflated the 2011 device costs used in TA314 (NICE 2014) to 2015 values (the actual date given in the submission is 1/1/16). In 2011, the average selling price for a CRT-D system was £12,293 and £11,752 for a replacement generator. However, the manufacturer appears to have entered the 2011 prices as 2014 (date of publication). See Table below for the 2015 and 2020 prices calculated if the TA314 prices are entered correctly as 2011. This generates slightly higher capital costs than those quoted by the manufacturer in both 2016 and 2020.

Table 3: Device Cost Inflation Comparison

Product	**Who?**	**2011 (TA314)**	**2015 (Avg 2.4%)**	**2020 (Avg 2.7%)**
system	EAC	£12,293	£13,515	£15,322
system	Manufacturer		£12,404	£14,075
generator	EAC	£11,752	£12,920	£14,648
generator	Manufacturer		£11,858	£13,455

The EAC will utilise 2020 values obtained from using the calculator rather than those given by the manufacturer.

Since MTG33, codes for 'attention to cardiac pacemaker of cardioverter defibrillator' (EY10B) and 'removal of cardiac pacemaker or cardioverter defibrillator' (EY09B) are no longer available. Only the cost of 'implantation of a cardioverter defibrillator with cardiac resynchronisation therapy with CC score 0-8' (EY01B) is available. As such, the EAC agrees with the manufacturer to use the day case/elective EY01B value for both de novo and replacement implantations. The NHS Tariff cost is £5,931 (NHS England and NHS Improvement, 2020), as submitted by the manufacturer, and the NHS Reference Cost is £3,342 (NHS England 2020). Of note, in 2015 the elective Tariff for this code was £14,984 and the Reference Cost was £15,120.

The EAC has not changed the original discount rate of 3.50%. The values used in the updated model are presented in Table 1 and Table 1.

Table 1: Economic Model Cost Inputs

Parameter		2016	2020	
Device Cost	De Novo	£12,404	£15,322	
	Replacement	£11,858	£14,648	
Complications*	Infection	£21,774	£24,686	
	Complication	£6,152	£6,975	
	Pocket	£18,010	£20,418	
			NHS Tariff Costs	**NHS Reference Costs**
Hospital Costs	De Novo	£6,201 (EY10B)	£5,931 (EY01B)	£3,342 (EY01B)
	Replacement	£4,700 (EY09B)	£5,931 (EY01B)	£3,342 (EY01B)
	Follow-up (WF01A)	£96	£78	£135

* Same values were used for complications relating to de novo and replacement procedures.

4. Results from updated model

Table 2 shows the overall costs and potential savings over 15 years, from using ENDURALIFE powered devices under the same assumptions as the original MTG33 model. Savings are presented for both NHS Tariff and NHS Reference Costs inputs for hospital costs, with original savings from MTG33 shown for comparison. Using NHS Tariff costs, as suggested by the manufacturer and used in MTG33, results in ENDURALIFE being £2,614 to £6,941 cost saving when compared to competitors.

The cost differences have increased since 2016, particularly for Tariff inputs. This is substantially due to the change in HRG codes available. Replacing both EY10B (de novo) and EY09B (replacement) with EY01B, means that initial implant procedures now cost £270 less, and replacements cost £1,231 more, than in the 2016 version of the model. This is most likely a quirk of the changes in coding rather than a real increase in replacement hospital costs. As noted above, EY01B values have decreased substantially since 2015. This may represent a real decrease in resource use per patient, such as high throughput centres, greater use of day case and outpatient procedures, and simpler surgical procedures.

Table 2: Model Results

Model	ENDURALIFE Cost	Medtronic Cost	Abbott/St Jude Cost	Saving against Medtronic	Saving against Abbott/St Jude
MTG33 (2016)	£28,234	£33,861	£30,354	£5,627	£2,120
NHS Tariff (2020)	£32,404	£39,345	£35,019	£6,941	£2,614
NHS Reference Costs (2020)	£29,679	£35,819	£31,992	£6,140	£2,313

5. Conclusion

Updating the original MTG33 model using the manufacturer's preferred cost update strategy (NHS Tariff costs and Bank of England inflation rates) results in a potential saving of £2,614 to £6,941 when ENDURALIFE powered devices are used compared to competitor devices. Using NHS Reference Costs (and Bank of England inflation rates) the potential savings range from £2,313 to £6,140. However, we do not believe that the original model assumptions are still valid. According to expert advice, there has been significant progress in CRT-D technologies since MTG33, invalidating the original battery life assumptions. This point is further strengthened by the change in CRT-D models that are available to the NHS. The change to national NHS Supply Chain purchasing of these devices since MTG33 suggests additional policy impacts on device capital costs. Also, the change in HRG codes used in 2016 and 2020 could have substantial impact on the calculated cost savings. In conclusion, the EAC opinion is that the economic modelling approach used in MTG33 in 2016 is no longer fit for purpose.

As such, the EAC recommends that NICE should consider updating the guidance to reflect the current state of CRT-D technologies' battery life and the costs of CRT-D devices in the NHS. Table 6 outlines the potential impact of such an update on the MTG33 (NICE 2017) recommendations.

Table 6: Potential Impact on Recommendations

MTG33 Recommendation	Potential Impact of the Update
The case for adopting ENDURALIFE-powered cardiac resynchronisation therapy-defibrillator (CRT-D) devices for treating heart failure is supported by the	The update might affect this recommendation. This will depend on whether currently available

published evidence. Extended battery life is of clinical and patient benefit and associated with fewer replacement procedures.	ENDURALIFE devices still offer extended battery life compared to present day comparators.
ENDURALIFE-powered CRT-Ds should be considered as an option in people offered CRT-D devices in line with NICE technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy.	The EAC does not envisage a guidance update to impact this recommendation, though it is possible depending on the outcomes of any updated cost analysis.
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 £2,120 and £5,627 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.	The update might affect this recommendation, depending on whether ENDURALIFE devices still offer an extended battery life with respect to comparators and on the price difference between ENDURALIFE devices and comparators.

6. References

Bank of England (2021) Inflation Calculator. Available at: https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator (accessed on 4 March 2021).

Boriani G, Merino J, Wright DJ, Gadler F, Schaer B and Landolina M (2018) Battery longevity of implantable cardioverter-defibrillators and cardiac resynchronization therapy defibrillators: technical, clinical and economic aspects. An expert review paper from EHRA. Europace 20: 1882-1897 doi: 10.1093/europace/euy066

Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L and Tavazzi L (2005) Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New England Journal Medicine 352(15):1539-49 doi: 10.1056/NEJMoa050496

Colquitt JL, Mendes D, Clegg AJ, Harris P, Cooper K, Picot J and Bryant J (2014) Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. Health Technology Assessment 18(56): 1-560 doi: 10.3310/hta18560

Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC (2014) Complications after cardiac implantable electronic device implantations: an analysis

of a complete, nationwide cohort in Denmark. European Heart Journal 35(18):1186-94 doi: 10.1093/eurheartj/eht511

Landolina M, Curnis A, Morani G, Vado A, Ammendola E, D'onofrio A, Stabile G, Crosato M, Petracci B, Ceriotti C, Bontempi L, Morosato M, Ballari GP and Gasparini M (2015) Longevity of implantable cardioverter-defibrillators for cardiac resynchronization therapy in current clinical practice: an analysis according to influencing factors, device generation, and manufacturer. Europace 17(8):1251-8 doi: 10.1093/europace/euv109

Landolina M, Morani G, Curnis A, Vado A, D'Onofrio A, Bianchi V, Stabile G, Crosato M, Petracci B, Ceriotti C, Bontempi L, Morosato M, Ballari GP, Gasparini M (2017) The economic impact of battery longevity in implantable cardioverter-defibrillators for cardiac resynchronization therapy: the hospital and healthcare system perspectives. Europace 19(8):1349-1356 doi: 10.1093/europace/euw176

Lau E.W. (2019) Longevity decoded: Insights from power consumption analyses into device construction and their clinical implications. Pacing and Clinical Electrophysiology 42(4):407–422 doi: 10.1111/pace.13642

National Institute of Health and Care Excellence (2017) ENDURALIFE-powered CRT-D devices for the treatment of heart failure. NICE Medical Technologies Guidance [MTG33] Available at: https://www.nice.org.uk/guidance/mtg33 (accessed on 9 March 2021)

National Institute of Health and Care Excellence (2014) Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure [TA314] Available at: https://www.nice.org.uk/guidance/ta314 (accessed on 9 March 2021)

NHS England and NHS Improvement (2020). 2020/21 National Tariff Payment System - 2020/21 Annex A: The national tariff workbook. Available at: https://improvement.nhs.uk/resources/national-tariff/#h2-202021-national-tariff-payment-system (accessed on 3 March 2021)

NHS England (2020) National Cost Collection: National Schedule of NHS costs - Year 2018-19 - NHS trust and NHS foundation trusts. Available at: https://www.england.nhs.uk/national-cost-collection/#ncc1819 (accessed on 13 February 2020)

Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL and Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators (2010) Cardiac-resynchronization therapy for mild-to-moderate heart failure. New England Journal of Medicine 363(25):2385-95 doi: 10.1056/NEJMoa1009540

Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC and Cleland JG (2007) The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. European Heart Journal 28(1):42-51 doi: 10.1093/eurheartj/ehl382

Background documents for this review

Hyperlinks for the background documents for this review report:

1. Medical technologies guidance document
2. Assessment report

   If applicable Additional work at consultation
3. Scope of assessment
4. A copy of the company information request regarding the technology
5. A list of expert advisers and their completed questionnaires on the MTG review
6. Executable cost model which aligns with the base case described in the MTG documents
7. If there is new evidence which is relevant to any of the clinical parameters in the model, the analyst should send the updated values.
8. Any relevant other documents which are not available on the NICE website.

Appendix 4 – changes to guidance

Table X: proposed amendments to original guidance

Section of MTG	Original MTG	Proposed amendment
Page 1, 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 £2,120 and £5,627 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.	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 £15,322 across different devices, using ENDURALIFE-powered CRT-Ds may save between £2,614 and £6,941 per patient using NHS Tariff costs and between £2,313 and £6,140 per patient using NHS Reference costs over 15 years through a reduction in the need for replacement procedures [2021]. This could save the NHS in England around £6 million in the first 5 years.
Page 25, 5.29		5.29 For the guidance review, the external assessment centre revised the model to reflect 2020 costs (original guidance values given in brackets). The main parameter changes were the costs of Enduralife-powered CRT-Ds which was assumed to be £15,322 (£12,404) and the costs associated with procedural complications which were estimated to be £24,686 (£21,774) for infection, £6,975 (£6,152) for complication requiring reintervention and £20,418 (£18,010) for device pocket issues. Hospital costs including procedural and follow-up costs were estimated to be £5,931 (NHS Tariff costs; EY01B) and £3,342 (NHS Reference costs; EY01B) for de novo procedures (£6,201; EY10B) and for replacement procedures (£4,700) and £78 (NHS Tariff costs) and £135 (NHS Reference costs) for follow up procedures (£96; WF01A). Base case results for the 2020 revised model shows the cost saving associated with

		ENDURALIFE-powered CRT-Ds was between £2,614 and £6,941 per patient using NHS Tariff costs and between £2,313 and £6,140 per patient using NHS Reference costs over 15 years. Further details of the 2020 revised model are in the revised model summary [2021].

References

Bank of England (2021) Inflation rates [online; accessed on 5 February 2021] https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator

Biffi M, Ammendola E, Menardi E, Parisi Q, Narducci ML, De Filippo P, Manzo M, Stabile G, Potenza DR, Zanon F, Quartieri F, Rillo M, Saporito D, Zacà V, Berisso MZ, Bertini M, Tumietto F, Malacrida M, Diemberger I. Real-life outcome of implantable cardioverter-defibrillator and cardiac resynchronization defibrillator replacement/upgrade in a contemporary population: observations from the multicentre DECODE registry. Europace. 2019 Oct 1;21(10):1527-1536

Clémenty N, Carion PL, Léotoing L, Lamarsalle L, Wilquin-Bequet F, Brown B, Verhees KJP, Fernandes J, Deharo JC. Infections and associated costs following cardiovascular implantable electronic device implantations: a nationwide cohort study. Europace. 2018 Dec 1;20(12):1974-1980

Feng XF, Yang LC, Tan LZ, Li YG. Risk factor analysis of device-related infections: value of re-sampling method on the real-world imbalanced dataset. BMC Med Inform Decis Mak. 2019 Sep 11;19(1):185

Gadler F, Ding Y, Verin N, Bergius M, Miller JD, Lenhart GM, Russell MW. Economic impact of longer battery life of cardiac resynchronization therapy defibrillators in Sweden. Clinicoecon Outcomes Res. 2016 Oct 31;8:657-666

Hauser RG, Casey SA, Gitter CB, Tang CY, Abdelhadi RH, Gornick CC, Stanberry L, Sengupta JD. Reliability and longevity of implantable defibrillators. J Interv Card Electrophysiol. 2021 Jan 2. Online ahead of print.

Landolina M, Morani G, Curnis A, Vado A, D'Onofrio A, Bianchi V, Stabile G, Crosato M, Petracci B, Ceriotti C, Bontempi L, Morosato M, Ballari GP, Gasparini M. The economic impact of battery longevity in implantable cardioverter-defibrillators for cardiac resynchronization therapy: the hospital and healthcare system perspectives. Europace. 2017 Aug 1;19(8):1349-1356.

Lau EW. Longevity decoded: Insights from power consumption analyses into device construction and their clinical implications. Pacing Clin Electrophysiol. 2019 Apr;42(4):407-422

Looi KL, Gavin A, Cooper L, Dawson L, Slipper D, Lever N. Outcomes of patients with heart failure after primary prevention ICD unit generator replacement. Heart Asia. 2019 Feb 28;11(1):e011162

Ludwig S, Theis C, Brown B, Witthohn A, Lux W, Goette A. Incidence and costs of cardiac device infections: retrospective analysis using German health claims data. J Comp Eff Res. 2018 May;7(5):483-492

McCarthy KJ, Locke AH, Coletti M, Young D, Merchant FM, Kramer DB. Outcomes following implantable cardioverter-defibrillator generator replacement in adults: A systematic review. Heart Rhythm. 2020 Jun;17(6):1036-1042

Munawar DA, Mahajan R, Linz D, Wong GR, Khokhar KB, Thiyagarajah A, Kadhim K, Emami M, Mishima R, Elliott AD, Middeldorp ME, Roberts-Thompson KC, Young GD, Sanders P, Lau DH. Predicted longevity of contemporary cardiac implantable electronic devices: A call for industry-wide "standardized" reporting. Heart Rhythm. 2018 Dec;15(12):1756-1763

NHS England and NHS Improvement (2020). 2020/21 National Tariff Payment System - 2020/21 Annex A: The national tariff workbook. [online; accessed on 29 January 2021] https://improvement.nhs.uk/resources/national-tariff/#h2-202021-national-tariff-payment-system

Paton MF, Landolina M, Billuart JR, Field D, Sibley J, Witte K. Projected longevities of cardiac implantable defibrillators: a retrospective analysis over the period 2007-17 and the impact of technological factors in determining longevity. Europace. 2020 Jan 1;22(1):149-155

Schmier JK, Lau EC, Patel JD, Klenk JA, Greenspon AJ. Effect of battery longevity on costs and health outcomes associated with cardiac implantable electronic devices: a Markov model-based Monte Carlo simulation. J Interv Card Electrophysiol. 2017 Nov;50(2):149-158

Weng W, Sapp J, Doucette S, MacIntyre C, Gray C, Gardner M, Abdelwahab A, Parkash R. Benefit of Implantable Cardioverter-Defibrillator Generator Replacement in a Primary Prevention Population-Based Cohort. JACC Clin Electrophysiol. 2017 Oct;3(10):1180-1189

Yang PS, Jeong J, You SJ, Yu HT, Kim TH, Sung JH, Lee SS, Park HD, Joung B. The Burden and Risk Factors for Infection of Transvenous Cardiovascular Implantable Electronic Device: a Nationwide Cohort Study. Korean Circ J. 2019 Aug;49(8):742-752

Zacà V, Narducci ML, Ziacchi M, Valente S, Pelargonio G, Tomasi C, Bandini A, Zingarini G, Calzolari V, Del Rosso A, Boggian G, Sabbatani P, Bonfantino MV, Malacrida M, Biffi M. Heart failure hospitalizations and costs in ICD/CRT-D recipients following replacement or upgrade: the DECODE registry. ESC Heart Fail. 2020 Sep 4;7(6):4377-83