Economic impact of introducing TYRX amongst patients with heart failure and reduced ejection fraction undergoing implanted cardiac device procedures: A retrospective model based cost analysis.

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Abstract

Background and Aims:

Infection is a serious and expensive complication of Cardiac Implantable Electronic Device (CIED) procedures. We performed a retrospective based cost analysis to estimate Trust level savings of using the TYRX[TM] antibacterial envelope as a primary prevention measure against infection in a tertiary referral centre in South London, United Kingdom.

Methods:

A retrospective cohort of heart failure patients with reduced ejection fraction undergoing Implantable Cardioverter Defibrillator (ICD) or Cardiac Resynchronization Therapy (CRT) procedures were evaluated. Decision-analytic modelling was performed to determine economic savings of using the envelope during CIED procedure versus CIED procedure alone.

Results:

Over a 12 month follow-up period following CIED procedure the observed infection rate was 3.14% (n=5/159). The average cost of a CIED infection inpatient admission was £41,820 and further to economic analysis, the additional costs attributable to infection was calculated at £62,213.94. A cost saving of £624 per patient by using TYRX[TM] during CIED procedure as a primary preventative measure against infection was estimated.

Conclusions:

TYRX™ would be a cost-saving treatment option amongst heart failure patients undergoing ICD and CRT device procedures based on analysis in the local geographical area of South London. If upscaled to the UK population, we estimate potential cost savings for the National Health Service (NHS).

Introduction

In recent decades, the number of Cardiac Implantable Electronic Device (CIED) procedures have increased substantially (1), consequent to growing indications for implantation based upon expanding evidence on improved morbidity and mortality (2-7), increased survival rates from ischaemic heart disease and an aging population (8). In accordance with this, numbers of CIED related infections have climbed with an estimated annual prevalence of 2-4% (9-11), despite best practise and vigilant infection-control standard operating protocols (12-15). Certain risk factors have been observed in relation to CIED infections including a medical history of diabetes, renal failure, heart failure and prior CIED infection, and use of anticoagulant or corticosteroid therapy. Additionally, Cardiac Resynchronisation Therapy (CRT) implants, revision or upgrade procedures, and procedures involving 3 or more pacing leads have increased infection risk (16-19). The risk of infection to any individual is most likely determined by the combination of risk factors that is present.

CIED infection is one of the most serious complications following the procedure characterized by high levels of patient related morbidity and mortality. Infections are associated with prolonged hospital admissions, extended antibiotic therapy and if the patient is a suitable candidate, recommended complete device extraction followed by re-implantation, the former being a major procedure with non-insignificant risks of serious complications including fatality (12, 14, 20, 21). All-cause mortality rates over a five year follow-up period have been reported as high as 35% (14, 19) and in cases of CIED endocarditis without concomitant device extraction, mortality rates range from 31-66% (13). Consequently, CIED infections contribute considerable financial burden to healthcare systems globally. Recent estimated costs attributable to a CIED infection related hospital

admission were $146,000 and £30,958 in the United States (US) and United Kingdom (UK) respectively (12, 21).

Given the significant clinical and financial burden of infection complications, ongoing primary prevention at the time of device procedure is paramount. The TYRX™ Absorbable Antibacterial Envelope (Medtronic plc, Mounds View, Minnesota)(22), is a sterile, single use multifilament knitted mesh composed of a polymer made of: glycolide, caprolactone, and trimethylene carbonate that houses the CIED generator within the subcutaneous pocket which elutes two antibiotics (rifampicin and minocycline) over at least a seven day period following device implantation and thereby providing a primary prophylaxis against infection. A non-absorbable version of the envelope was previously available and in several observational studies demonstrated an infection reduction rate between 69-100% with associated cost-effectiveness (11, 23, 24). A prospective randomized controlled trial determining the efficacy of the absorbable TYRX™; the World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT)(25) is currently underway with highly anticipated results.

This paper describes an economic model developed to demonstrate the potential financial savings of using TYRX™ as a preventative measure against infection within a retrospective cohort of Heart Failure patients with reduced Ejection Fraction (HFrEF) (26) undergoing CIED procedures inclusive of Implantable Cardioverter Defibrillator (ICD) or CRT, to a single National Health Service (NHS) Foundation Trust within South London, UK and its local Clinical Commissioning Group (CCG).

Methodology

Retrospective Audit

A retrospective audit of all ICD and CRT procedures in patients with HFrEF within two local geographical residential areas of a single tertiary referral institution and high volume device implantation centre (Guy's and St Thomas' NHS Foundation Trust, London, UK) was registered, approved and conducted between 1st January 2014 and 31st September 2017. St Thomas' Hospital is a large NHS teaching hospital in South London. It acts as a tertiary referral centre for cardiovascular disease with services covering cardiology, cardiothoracic surgery and congenital heart disease for both paediatric and adult populations. The

estimated population of the 2 local geographical areas is approximately 575,000 people. Both are socially deprived areas based on UK local authority data (40th and 44th most deprived areas respectively). Approximately 60% of this population is Caucasian and 25-30% Black ethnic origin. Procedures were inclusive of new or de novo implant, generator change and upgrades and performed by appropriately skilled operators. Data collected was inclusive of those specific to the device procedure in addition to patient demographics, co-morbidities, prescribed medications and health care utilization to the Trust within a 24 month window; 12 months pre and post device procedure. CIED infection was defined by a hospital admission within the first 12 months following device procedure requiring a prolonged course of intravenous antibiotics with or without a device extraction procedure. Infections were identified through a combination of searching a purpose built Trust Extraction Database, which contributed to the European Lead Extraction Registry (19, 27) and using the 10th Edition of the World Health Organization (WHO) International Classification of Disease (ICD) discharge code for the admission relating to the CIED infection containing ICD-10 code T82.7 within the Trust's information systems.

Infection-control Protocol

The Trust's infection-control protocol when performing CIED procedures throughout the period of January 2014 to September 2017 is detailed in our technical appendix and we assume 100% compliance. The TYRX™ envelope was not in use during ICD and CRT related device procedures within the Trust during the time period analysed.

Economic analysis

We developed a decision-analytic model seeking to assess the expected economic impact of introducing the TYRX™ Absorbable Antibacterial Envelope whereby the primary aim is to reduce infection rates after CIED procedures. The perspective of the model is within a single NHS Foundation Trust. The time horizon captured in the analysis was set to one year to be consistent with the scope of the study. The model consists of two mutually exclusive pathways; CIED procedure with TYRX™ versus CIED procedure alone without TYRX™ (see Figure 1). Mortality was not included as there were no deaths observed within the CIED infection group during the first 12 months post discharge. Costs of healthcare utilization in

the 12 months post CIED procedure were captured subsequent to the date of discharge following the CIED procedure, therefore the procedural costs relating to this were not included in the total cost estimation. The model was probabilistic to capture the joint impact of parameter uncertainty. A Monte Carlo simulation consisting in 999 iterations was conducted in Microsoft Excel. The model parameters were cost of infection, baseline infection risk and odds ratio of infection with TYRX™ relative to current practice. We used an odds ratio of 69% based on a recent meta-analysis (28)to derive the probability of infection within the TYRX™ group. A Gamma distribution was assumed for Infection cost. A log normal distribution was selected for the odds ratio of infection with TYRX™ relative to current practice. For both groups, the procedural costs were assumed to be equivalent, therefore were not included in the model.

The probability of developing infection for the no-TYRX™ branch was defined as the proportion of procedures that resulted in an infection episode throughout the 12-month follow-up period in the 159 procedures cohort. In the absence of an experimental group, we assumed infection risk using TYRX reduced by the odds ratio obtained from a recent meta-analysis (29). We derived the probability of infection in the TYRX-group by combining the odds ratio for infection with TYRX and the odds of infection without TYRX observed from the retrospective audit (please refer to our Technical Appendix for further detail). The parameters of the model are presented in Table 1.

Cost Analysis

An estimated cost for each patient for the 12-month period following their device procedure was calculated. This was inclusive of inpatient admissions, outpatient department (OPD) and Accident and Emergency (A&E) department visits and Community Heart Failure Nurse visits. As HFrEF patients are frequently associated with multiple co-morbidities, we felt it was vitally important to calculate and present the 'total' expense of their 12-month post device procedure journey rather than just the cardiac related costs. In

addition to the 'total' 12-month cost, we are been able to scrutinise our cost data in great detail enabling us to calculate costs related specifically to cardiac and non-cardiac health care utilization. Unlike previous published works, which used financial data derived from reference costs, our inpatient admission, A&E and OPD department related financial data were derived from patient level costing and represent the actual cost to the Trust. Inpatient admission costs represented the entire outlay of the hospital stay, including device, staffing, overheads and diagnostic testing. We also recorded hospital income for patient care, based on nationally and locally agreed reimbursement tariffs but they have not been used further in our analysis or reported results. General Practise (GP) healthcare utilization was not reported and, because their costs are fixed, they have not been included in our analysis. Community Heart Failure Nurse visit costs are separately commissioned and available to the Trust drawn from reference costings. Overall, community related costs contribute less significantly to the overall 12-month care pathway post device procedure in contrast to inpatient admissions. Missing costs data was observed for 9% of inpatient admissions, 6% of OPD visits and 3% of A&E attendances. For missing inpatient costs we used the predicted values from a multi-variable linear regression model which included bed-days, critical care days, type of admission and whether a CIED procedure was performed during the admission. We added some random noise to the imputed values (with a standard deviation equal to the root-mean-square error), to give some variability around the regression line. For the missing A&E data, we used HRG-level reference costs supplied by the trust. For the majority of the missing outpatient data we again used reference costs and where this wasn't possible, we simply used median costs. A cost of £719 for the TYRX^{TM} envelope was used for analysis purposes, which has been previously quoted and published in health economic literature (22).

Estimation of costs attributable to infection

We undertook regression analysis of total costs to allow adjustment for patient case-mix in the estimation of the cost attributable to infection. We applied Generalised Linear Modelling following recommendations by Mihaylova et al (30) and used the Park test to select the distribution. Given the limitations of the sample size we considered a linear and a log link (additive and multiplicative model). We assessed the robustness of estimation of infection-attributable cost through two sensitivity analyses.

- We applied an ordinary least squares (OLS) model in place of the GLM model in combination with bootstrapping to quantify uncertainty.
- We estimated the cost of infection through attribution of resource use deemed to have arisen from infection for the five patients with an infection.

We also conducted a scenario analysis on the TYRX ™cost in order to determine the threshold of positive savings to the NHS. The reported market price of the device was varied ± 50%. We report the breakeven price of TYRX™. All the statistical analyses were conducted on Stata SE 15 ®. Further details on these methods are provided in the Technical Appendix.

Statistical Analysis

The demographics, device procedural details, comorbidities and other associated risk factors for CIED infection were compared among the two patient groups; with and without infections and presented using descriptive statistics with measures of frequency, central tendency and variation.

Results

Device Infection Rate

One hundred and fifty nine ICD and CRT device related procedures occurred in 157 HFrEF patients between 1st January 2014 and 31st September 2017 within 2 specified catchment geographical areas for the Trust (see Table 2). Two patients underwent 2 separate procedures as a result of upgrade from ICD to CRT-D, each with separate 12-month follow-up periods that did not overlap within the 45-month time period, therefore accounting for 159 procedures. 5 patients developed a CIED infection within 12 months of their device procedure requiring prolonged inpatient admission and device extraction followed by re-implantation, resulting in an infection rate of 3.14%. All 5 patients had confirmed microbiology evidence of CIED infection with either positive blood cultures and/or pacing lead tip cultures for typical bacterial organisms; 2 Staphylococcus Aureus, 2 Staphylococcus Epidermis and 1 Enterococcus Faecalis. All 5 patients underwent full CIED system extraction

during the CIED infection related admission followed by re-implant procedures prior to discharge. The average length of stay for the CIED infection related admission was 43.6 days, with the largest contributors to the total admission cost being inpatient bed days (inclusive of critical care bed days)27%, devices 17%, Trust overheads 16% and finally medical staffing costs at 12%. Patient demographics, co-morbidities and specifics of the device procedure for both groups (those with and without a CIED infection) are shown in Table 3.

Cost of Infection

Using the raw cost data, excluding costs relating to the CIED procedural admission (as already detailed in our methodology), the average total 12-month post device procedure healthcare cost was £13,326. The unadjusted difference between mean costs of non-infected and infected patients from the raw cost data was £59,048.82. The average cost of attributed individual resource use (n=5) relating to a CIED infection was £41,820.40 (range £28,377-£56,498). The distribution of total costs was strongly right-skewed (Figure 2). The modified Park test indicated the Gamma distribution best fit the data. Link tests indicated a linear link (additive model) was superior to a log link. Table 4 presents the results of alternative approaches to the estimation of 'total' costs attributable to infection. Infection costs were highest when estimated using GLM and lowest when estimated using attribution of individual resource use. Additional costs attributable to infection costs were £62,213.94 [SE £16,697.81] in the base case (GLM). When analysed for cardiac related costs only, the additional costs attributable to infection were £49,541.25 [SE £10,707.48] in the base case (GLM).

Economic analysis

Table 4 also summarises the results of the economic impact assessment. Utilising a base-case device price of £719 and infection costs estimated from GLM, TYRX™ generated savings of £624 per procedure. In sensitivity analysis savings were £514 and £184 per

procedure using infection costs estimated from the OLS model and direct attribution of resource use, respectively. The breakeven price for the TYRX^{TM} envelope was £1,361.

Discussion

We observed an infection rate of 3.14% (n=5/159) amongst a HFrEF population undergoing ICD and CRT device related procedures. The average cost of a CIED infection inpatient admission was £41,820 and further to GLM analysis, the additional costs attributable to infection was calculated at £62,213.94 ('total' costs) and £46,770 (cardiac related costs). Our economic analysis determined cost savings between £184 and £624 by using the TYRX^{TM} absorbable envelope at the time of procedure as a primary preventative measure against CIED infection.

 Accurate figures of the scale of CIED infection and their associated costs are not known within the UK, however predictions on continued growth in the number of CIED procedures, particularly within older and comorbid populations mean that these figures are projected to increase. Definitions of what entails a CIED infection and during what timeframe of follow-up varies in the literature, making comparison challenging, however the observed rate of infection in our cohort within 12 months of the device procedure, 3.14%, falls within the range published in current literature (2-4% annual prevalence). It is possibly not surprising, that our infection rate was nearer to the top end of this range, given that we specifically studied a 'high risk' group; patients with HFrEF, of whom 80% had a CRT device and 44% underwent a recurrent procedure (generator change or upgrade). As Table 2 demonstrated, significant comorbidities were substantially prevalent within our cohort, with traditional infection risk factors of diabetes, renal failure and COPD featuring prominently.

To really understand the financial implications of CIED infections, the first key measures are to define a dedicated geographical area and utilize accurate and validated cost data. This project addresses these specifically; we created a purpose-built database able to capture both community and secondary care health utilization for patients with HFrEF and implanted ICD or CRT devices within a pre-defined local residential geographical location.

Our cost data has been obtained directly from the Trust Finance department and provides the actual cost incurred by the Trust at an extremely accurate and detailed level for any individual patient and any individual healthcare transaction. We have been able to provide a robust 'total' cost estimate for any patient within our cohort, which more accurately represents the entire cost of their healthcare journey within 12 months of their device procedure but are also able to interrogate our cost data by type of healthcare utilization (inpatient, A&E etc) or whether this is cardiac or non-cardiac related. Having reviewed the literature, we believe this is uniquely different to any previously published work in this area.

Previous estimates of the cost of CIED infection to health care systems globally within the last decade vary from $146,000 (US), £30,958 (UK) and €20,211-23,237 (France) (12, 21, 31). Methodologies to determine cost estimates differed across these studies, all encompassed an estimated cost for a hospital admission relating to the CIED infection, however the acquisition of cost data varied from a cost-to-charge ratio, diagnosis related group (DRG) coding (similar to income reimbursements paid to NHS service providers) to the use of reference costings. Another important difference to highlight between our work and these studies is that they were all inclusive of single and dual chamber pacemakers for treatment of bradyarrhythmia, which incur a lower device tariff/cost compared to ICD or CRT-D for the replacement device procedure and one study included CIED infections that were medically managed without system extraction. All these factors in synergy may account for the higher comorbidity-adjusted estimate of cost attributable to CIED infection related hospital admission in our cohort; £61,585. The fact that we also observed an inflated cost when adjusted to include only the cardiac related costs specifically; £49,541.25, reinforces our results and the strengths of our costing methodology. Discrepancies could also be explained by un-observed cofounders or due to a lack of earmarking of additional resource costs within the infection group to that of infection costs.

One of the main limitations of this report is the small sample size. In total, 5 patients from our limited cohort experienced a CIED infection within 12 months of their device procedure, therefore deriving definitive conclusions from this analysis should not be done without due care and attention. Alongside the small sample size, which had implications on the robustness and accuracy of our estimates, the fact that this was retrospective data with the

lack of a control or placebo group, necessitated making strong assumptions on similarities between groups to perform economic analysis to estimate cost savings from the intervention of using the TYRX™ envelope. Our first assumption was the probability of infection within the TYRX™ group, in the absence of results from the awaited randomized controlled WRAP-IT (25)trial on CIED infection rate reduction. We used reduction of relative risk of 69% previously published in the literature (29) to derive the probability of infection within the TYRX™ group. This calculation was made under the assumption of enough similarity amongst studies' population that enables reverse engineering combining primary and secondary data. Despite this, the structural sensitivity analysis on cost estimation demonstrated cost savings, although there is a marginal difference among approaches. Whilst our economic model analysis calculated a cost saving of approximately £600 per patient using TRYX™ as a preventative measure against infection, this was observed in a 'high risk' studied group and therefore it cannot be assumed that when applied to patients without heart failure or those undergoing bradyarrhythmia pacemaker procedures, the same savings effect would be observed.

However, using our methods of a fixed geography, unique costings; which provide full and accurate costs at a Trust level, and using our calculated cost saving of £624 per procedure, suggests that using the TYRX^{TM} envelope would result in reductions in costs to the NHS. Based on national figures in 2015-2016 (32), whereby 295 new or de novo ICD and CRT device implants per million population were performed In England, potential savings to the NHS could be estimated at over £9,700,000. This figure is underestimated as it is not inclusive of generator change and upgrade procedures or those from the Welsh, Scottish and Northern Ireland populations. Additionally, the use of the TYRX^{TM} would have resulted in an estimated reduction in the infection rate to 1.02%, meaning 3 out of the 5 patients with CIED infection observed in our cohort would not have experienced an infection with a consequent reduction in the associated morbidity and mortality.

Conclusion

Overall, our study findings suggest that the TYRX™ envelope would be a cost-saving treatment option amongst HFrEF patients undergoing ICD and CRT device procedures within the local geographical area of the Trust.

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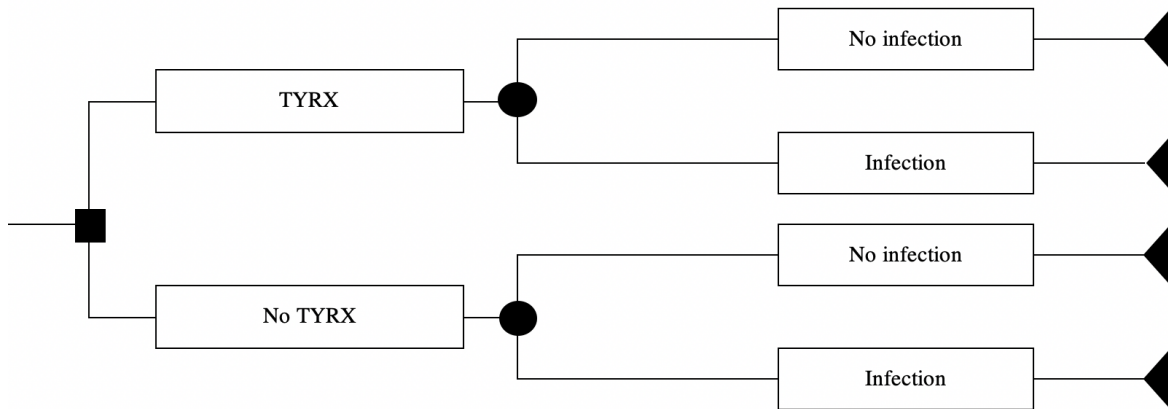
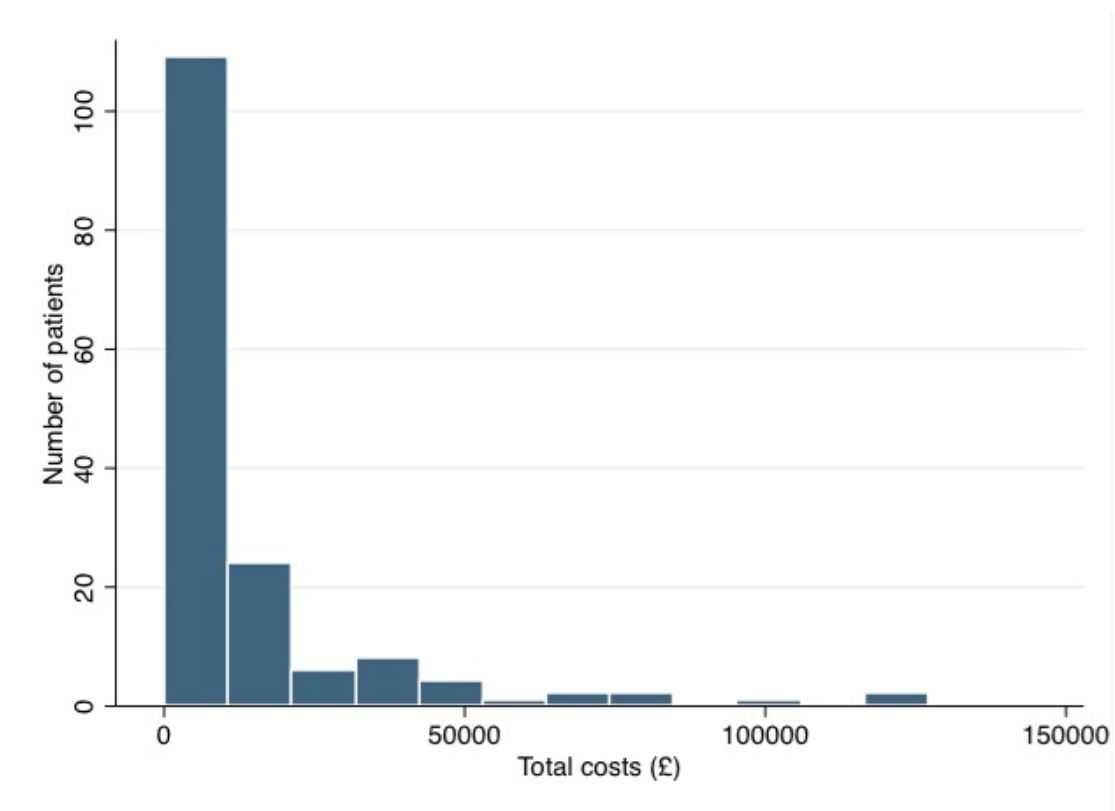*Figure 1. Decision analytic model developed to analyse the expected economic impact of introducing TYRX.*

Figure 2. Histogram of total costs after 12-month follow-up (n=159).

Table 1: Parameters of economic model

Parameter	Value	Source
Infection cost	£61,585.76	GLM estimate
Mean cost of TYRX	£719.00	Reported market price
Probability of infection in the No TYRX group	3.205%	Retrospective data
Odds ratio of TYRX vs no TYRX	0.31	Koerber et al
Probability of infection in TRX group	1.0161%	Derived from Koerber et al and retrospective data

Table 2: ICD and CRT device procedures in HFrEF patients between 1st January 2014 and 31st September 2017.

	ICD	CRT-P	CRT-D	Total
Generator Change	4	11	29	44
Upgrade	-	16	10	26
New Implant	28	19	42	89
Total	32	46	81	159

Key: ICD= Implantable Cardioverter Defibrillator, CRT-P= Cardiac Resynchronisation Therapy Pacemaker, CRT-D= Cardiac Resynchronisation Therapy Defibrillator.

Table 3: Baseline characteristics, comorbidities and CIED risk factors in patients with and without CIED infections (n/%).

	Infection Group (n=5)	Non-Infection Group (n=152)
Age (mean/range)	67 (54-82)	68 (22-92)
Gender: Male	4 (80%)	115 (76%)
Anaemia	1 (20%)	29 (19%)
Atrial Fibrillation	2 (40%)	79 (52%)
CAD	2 (40%)	79 (52%)
Malignancy	0 (0%)	22 (14%)

COPD	3 (60%)	47 (31%)
Dementia	0 (0%)	5 (3%)
Diabetes	2 (40%)	72 (47%)
Hypertension	4 (80%)	118 (78%)
Sleep Apnoea	0 (0%)	23 (15%)
CKD	2 (40%)	57 (38%)
Stroke	0 (0%)	5 (3%)
Valve Disease	4 (80%)	49 (32%)
Myocardial Infarction	3 (60%)	64 (42%)
Mood Disorder	0 (0%)	23 (15%)
Anticoagulation Therapy	2 (40%)	80 (53%)
Generator Change/Upgrade Procedure	2 (40%)	68 (45%)
Presence of Defibrillation Lead	5 (100%)	106 (70%)

Key: CAD= Coronary Artery Disease, COPD= Chronic Obstructive Pulmonary Disease, CKD= Chronic Kidney Disease.

Table 4. Sensitivity analysis on cost estimation method.

Method of cost estimation	Total cost (se)	Infection Cost (se)	Expected savings (95% CI)
GLM	13,193.64 (979.57)	62,213.94 (16,967.81)	624.09 (597.00 - 651.16)
OLS + Bootstrap	13,385.04 (54.06)	58,841.7 (644)	514.23 (484.74 - 543.71)
Attribution of resource use	13,425.61* (1,716.69)	41,820.4** (13,257.28)	184.67 (164.68 - 204.67)

*Average cohort total cost
** Average cost of attribution of resource use in only infected patients.
Key: GLM: Generalised Linear Model. OLS: Ordinary Least Squares. se: standard error. CI: Confidence Interval.

<u>Technical Appendix</u>

<u>Infection-Control Protocol</u>

Below is a detailed infection-control protocol used in the Trust between 1st January 2014 and 31st September 2017 prior to any CIED related procedure.

a) Methicillin-resistant Staphylococcus Aureus (MRSA) screening

Performed on all patients prior to device procedure via nasal and groin swabs. In the event of MRSA carriage detection, topical eradication therapy comprising nasal mupirocin and 4% chlorhexidine skin wash was implemented for 5 days before the patient was re-screened.

b) Antibiotic cover

Intravenous Flucloxacillin 2g or Vancomycin 1g (in the event of penicillin allergy) was administered within 30 minutes prior to any device related procedure. In the event of an urgent procedure in an MRSA carriage positive status, intravenous Teicoplanin 400mg was administered. It was operator-dependent preference to administer 80mg Gentamicin directly into the pocket at the point of pocket closure. Antibiotics were not continued post-procedure.

c) Skin preparation

Excess hair over the intended surgical site was removed using electrical shavers only. Skin was sterilised using a 2% chlorhexidine gluconate/70% isopropyl alcohol solution within a preloaded applicator.

d) Surgical scrubbing technique

Scrubbing was performed for a minimum duration of 2 minutes with 4 separate individual scrubs recommended, one of which included the use of a sterile single use nail brush. Double gloving was mandatory during draping, after which the outer gloves were removed prior to skin incision.

e) Diathermy

Used in all generator change or upgrade procedures. It was operator-dependent preference for any new or de novo implant procedures.

f) Sutures and wound dressing

Antibacterial-coated sutures were not in use at the Trust during the studied time period. Standard vicryl and subcuticular sutures were employed. Wound dressings were left intact for 3-5 days post procedure.

Calculation of probability of infection

Under the assumption that the odds ratio for infection with TYRX is 0.31 [95% CI, 0.17 − 0.58][1], we derived the probability of infection with TYRX by calculating the odds of the "exposed group" using the reported odds ratio and the odds of the "unexposed group" observed in the retrospective audit.

More generally, consider the definitions of odds and odds ratio:

$$odds \ of \ outcome = \frac{probability \ of \ outcome}{1 - probability \ of \ outcome} \tag{1}$$

$$odds \ ratio = \frac{odds \ of \ exposed}{odds \ of \ unexposed} \tag{2}$$

We rewrite Eq 2 to calculate the odds of exposed:

$$odds \ of \ exposed = odds \ ratio * odds \ of \ unexposed \tag{3}$$

Then we rewrite Eq 1 to calculate probability of outcome.

$$probability \ of \ outcome = \frac{odds \ of \ outcome}{1 + odds \ of \ outcome} \tag{4}$$

Solving for Eq 3 (using the figures mentioned above) and replacing the result in Eq 4, we calculated probability of infection in the TYRX group.

[1] Koerber, S., Turagam, M., Winterfield, J., Gautam, S. and Gold, M. (2018). Use of antibiotic envelopes to prevent cardiac implantable electronic device infections: A meta-analysis. Journal of Cardiovascular Electrophysiology, 29(4), pp.609-615.

$odds\ of\ infection\ in\ no-TYRX\ group$

$$= \frac{probability\ of\ infection\ in\ no-TYRX\ group}{1-probability\ of\ infection\ in\ no-TYRX\ group} = \frac{0.032051}{1-0.032051}$$

$$= 0.033112583$$

$odds\ of\ infection\ in\ TYRX\ group$

$$= Koerber's\ odds\ ratio * odds\ of\ infection\ in\ no-TYRX\ group$$

$$= 0.31 * 0.033112583 = 0.010264901$$

$$probability\ of\ infection\ in\ TYRX\ group = \frac{odds\ of\ TYRX\ group}{1+odds\ of\ TYRX\ group}$$

$$= \frac{0.010264901}{1+0.010264901} = 0.01016 = 1.02\%$$

Specification of GLM

GLM provides flexibility in the choice of distribution and the specification of the relationship between the dependent and independent variables which better accommodates some of the characteristics of the distribution of cost data such as heteroscedasticity. Selection of the distribution was confirmed by the modified Park test. Given the limitations of the sample size we evaluated a linear and a log link (for an additive or multiplicative specification of dependent variables) using the Pregibon, Pearson and Hosmer & Lemeshow link tests. Fractional polynomials were assessed to guide the best specification of age, which was the only continuous variable. The results of such assessment indicated the optimal polynomial form for age was in cubic terms. The model was defined as follows:

$$Total\ costs_i = \beta_0 + \beta_1 Infection_i + \beta_2 Age_i^3 + \beta_3 Age_i^3 \ln(Age_i) + \beta_4 Sex_i + \beta_5 COPD_i + \beta_6 Diabetes_i$$
$$+ \beta_7 Renal\ Failure_i + \beta_8 Anticoagulation\ Medication_i + \beta_8 Recurrent\ surgery_i + u_i$$

Where infection, sex, COPD, diabetes, renal failure, anticoagulation medication and recurrent surgery are dummy variables defined as 1 if that patient experienced infection, was a male, had any of the comorbidities (chronic obstructive pulmonary disease (COPD), diabetes, renal failure or anticoagulation medication), or underwent upgrade or box change

surgery; and 0 otherwise. U is the error term with a Gamma distribution. The corresponding beta-values are presented in Table 1.

Table 1. Summary of GLM estimated coefficients.

Variable	Coefficient (P-values)
Infection	62,213.94 (0.000)
Age^3	-0.2795816 (0.227)
Age^3 * ln(Age)	0.0610762 (0.221)
Sex	2,568.671 (0.002)
COPD	3,403.272 (0.133)
Diabetes	5,532.019 (0.007)
Renal failure	6,588.921 (0.012)
Anticoagulation medication	3,776.257 (0.001)
Recurrent surgery	-2,910.15 (0.004)
Intercept	8,250.25 (0.214)

Selection of OLS model for bootstrap replicates

We undertook bootstrapping to quantify uncertainty around the estimate of the cost of infection using an OLS model. In the base case GLM model we favoured a parametric approach to the quantification of uncertainty for two reasons: the GLM model was less likely to be incorrectly specified (which may violate parametric assumptions); bootstrapping can encounter convergence problems when undertaken with GLM requiring maximum likelihood estimators and regression models at risk of collinearity. OLS estimation identifies and drops perfectly collinear regressors.[2]

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[2] Santos Silva, J. and Tenreyro, S. (2010). On the existence of the maximum likelihood estimates in Poisson regression. Economics Letters, 107(2), pp.310-312.