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ORIGINAL RESEARCH

Cost-effectiveness of TYRX absorbable antibacterial envelope for prevention of cardiovascular implantable electronic device infection

Gemma Kay[a], Elizabeth L. Eby[b], Benedict Brown[c], Julie Lyon[d], Simon Eggington[c], Gayathri Kumar[a], Elisabeth Fenwick[a], M. Rizwan Sohail[e] and David Jay Wright[f]

[a]ICON Health Economics and Epidemiology, Abingdon, UK; [b]Medtronic plc, Mounds View, MN, USA; [c]Medtronic International Trading Sàrl, Tolochenaz, Switzerland; [d]Medtronic, Ltd, Watford, UK; [e]Divisions of Infectious Diseases and Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA; [f]Liverpool Heart and Chest Hospital, Liverpool, UK

ABSTRACT

Aims: Infection is a major complication of cardiovascular implantable electronic device (CIED) therapy that usually requires device extraction and is associated with increased morbidity and mortality. The TYRX Antibacterial Envelope is a polypropylene mesh that stabilizes the CIED and elutes minocycline and rifampin to reduce the risk of post-operative infection.

Methods: A decision tree was developed to assess the cost-effectiveness of TYRX vs standard of care (SOC) following implantation of four CIED device types. The model was parameterized for a UK National Health Service perspective. Probabilities were derived from the literature. Resource use included drug acquisition and administration, hospitalization, adverse events, device extraction, and replacement. Incremental cost-effectiveness ratios (ICERs) were calculated from costs and quality-adjusted life-years (QALYs).

Results: Over a 12-month time horizon, TYRX was less costly and more effective than SOC when utilized in patients with an ICD or CRT-D. TYRX was associated with ICERs of £46,548 and £21,768 per QALY gained in patients with an IPG or CRT-P, respectively. TYRX was cost-effective at a £30,000 threshold at baseline probabilities of infection exceeding 1.65% (CRT-D), 1.95% (CRT-P), 1.87% (IPG), and 1.38% (ICD).

Limitations and conclusions: Device-specific infection rates for high-risk patients were not available in the literature and not used in this analysis, potentially under-estimating the impact of TYRX in certain devices. Nevertheless, TYRX is associated with a reduction in post-operative infection risk relative to SOC, resulting in reduced healthcare resource utilization at an initial cost. The ICERs are below the accepted willingness-to-pay thresholds used by UK decision-makers. TYRX, therefore, represents a cost-effective prevention option for CIED patients at high-risk of post-operative infection.

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Cost-effectiveness; cardiovascular implantable electronic device; infection; antibacterial envelope

Introduction

Complications associated with cardiovascular implantable electronic devices (CIED) include infections and device migration or erosion. CIED-related infections are difficult to diagnose and treat, can be associated with significant morbidity and prolonged hospital stay, and carry a recommendation of complete device explantation[1,2]. Systemic infection associated with CIED can be life-threatening with all-cause mortality rates of up to 35% reported over follow-up periods of up to 5.5 years[1]. Device explantation is a major procedure and carries a risk of mortality or serious complications[1,3]. Besides patient-related morbidity and mortality, management of CIED infections has considerable financial impact. The average hospital charge for a CIED infection in the US was estimated to be $146,000 in 2009[4], and the average cost of a CIED infection in the UK National Health Service (NHS) has been estimated at £30,958 (publication date 2014), taking into account extended hospital stay, device explantation, re-implantation, and antibiotic use[3].

Device infection occurs in 1–2% of CIED recipients overall[3,4], and in 3–4% of high-risk patients[5,6]. The number of cases is somewhat uncertain, but appears to be increasing due to the rising number of CIED implantations, proportionately increasing the use of CRT devices which entail a more complex implant procedure, and higher prevalence of comorbid conditions in CIED recipients[1,4]. Given the high clinical and economic burden of CIED infections, prevention is of prime importance[1].

The TYRX™ Absorbable Antibacterial Envelope (Medtronic plc, Mounds View, MN)[7] is a sterile, single-use surgical mesh envelope that houses the CIED generator when implanted into the pocket. A non-absorbable version of the envelope was previously available; however, this was discontinued following the launch of the absorbable envelope. It provides prophylaxis against infection by eluting the antibiotics

CONTACT Gemma Kay gemma.kay@iconplc.com ICON Plc., 100 Park Drive, Milton Park, Abingdon OX14 1RY, UK
Supplemental data for this article can be accessed here.

rifampin and minocycline for a minimum of 7 days in the generator pocket environment before being fully absorbed by the body. It also helps to stabilize the device by lowering the risk of device migration. Efficacy of the envelope based on prospective randomized trials is yet to be reported, although this is currently under investigation in two clinical trials: the World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT), a randomized, controlled trial comparing CIED infection rates and complications over a 12-month period for absorbable antibacterial envelopes vs no envelope (NCT02277990)[8]; and in the Perioperative Antibiotic Therapy to Prevent Cardiac Implantable Electronic Device Infections (ENVELOPE) trial (NCT02809131)[9]. However, effectiveness of the TYRX Antibacterial Envelope has been studied in a series of observational trials among patients at high-risk for CIED infection[6,10–13] with the first generation of non-absorbable envelopes and more recently with the absorbable envelope[10]. In these studies, patients with TYRX Envelopes experienced a reduction of 69–100% in CIED infections compared to patients who underwent CIED implantation without the envelope.

This paper describes a cost-effectiveness model developed to assess the cost implications and health outcomes associated with TYRX Absorbable Antibacterial Envelopes vs current standard of care (SOC) in the prevention of infection post-CIED implantation from the NHS perspective. The paper presents the economic value of utilizing TYRX, compared with an infection control protocol with no Envelope, for patients undergoing a *de novo* or replacement implantation with a cardiac resynchronization therapy defibrillator (CRT-D), cardiac resynchronization therapy pacemaker (CRT-P), implantable pulse generator (IPG), or implantable cardioverter defibrillator (ICD) in both the short and longer term.

Methods

Model structure

Given the short-term nature of the decision problem (i.e. the short-term impact of the Envelope on the risk of infection), a decision tree with a time horizon of 1 year was selected as the appropriate model structure. However, best practice in cost-effectiveness modelling is to establish the costs and benefits associated with an intervention for the period of time over which these are expected to differ. As such, following on from the decision tree, patients were allocated long-term costs and benefits corresponding to their status at 12 months. This ensured that any differences in lifetime costs and benefits due to mortality differences between treatments were captured. The decision tree model (Figure 1) was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA) to assess the cost-effectiveness of TYRX Absorbable Antibacterial Envelopes vs SOC infection prophylaxis for each of the CIEDs of interest (CRT-D,CRT-P,IPG, ICD for patients at "high-risk" of infection, as well as for those at lower risk of infection ("all-comers").

Each event following the initial procedure was characterized by a node that occurred with a given probability, and each branch represented a mutually exclusive pathway. The total costs and pay-offs associated with either treatment option were calculated by multiplying the pathway probabilities by the corresponding costs and outcomes and summing the expected costs and pay-offs. In the absence of literature on sub-group-specific data relating to events other than CIED infections, these were assumed not to differ across treatments or risk groups. The pathway probabilities, therefore, differed between treatment arms and sub-groups only to the extent that they were conditional on the initial infection risk.

SOC was defined as one course of pre-operative antibiotic prophylaxis only. In addition, patients in the TYRX arm received the envelope during the procedure. Following the procedure, all patients were at risk of experiencing a CIED infection (Figure 1).

Model inputs

The tables of model inputs are given in the Supplementary material.

Probability of infection

Infection rates associated with SOC for "high-risk" patients were obtained from two prospective analyses[5] and four

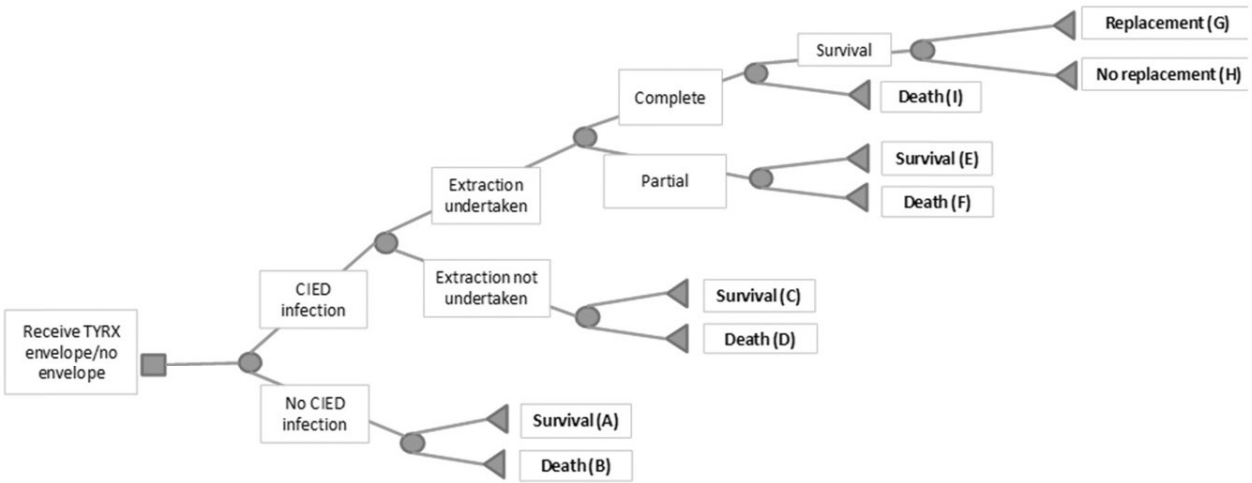

Figure 1. Decision tree analysis of using TYRX for the prevention of infection post-CIED implantation.

retrospective observational studies of TYRX[5,6,11–13]. For the "all-comers" category, probabilities of infection associated with SOC were obtained from the Shariff *et al.*[12] study. Absolute probabilities of infection for TYRX were also available from these studies. Rather than use these values in the model directly, which would mean they were independent of the probability of infection for SOC, a relative risk associated with the use of TYRX was calculated and applied to the probability of infection with SOC. An assumption was made that the relative risk would apply consistently across all risk groups, with the difference in infection rates driven only by the difference in the baseline risk (probability of infection with SOC). As such, the relative risk was determined by pooling the total populations (*N*) and number experiencing an infection (*n*) across all studies for SOC and independently for TYRX. The data and calculation method used to derive this mean relative risk value (0.163) are reported in the Supplementary material. Applying the relative risk to the baseline probability of infection with SOC for each study/pooled analysis provided estimates of the probability of infection for TYRX. Device-specific infection rates for the high-risk population were not reported in the literature, and, as such, baseline infection rates were assumed to be equivalent across device types. Clinical input from a UK expert was sought to validate data inputs and assumptions.

Infection management

Complete removal of the device and leads is recommended for major CIED infections[1,14]. An estimated 3–15% of patients refuse or are considered medically unfit for device extraction[1]. An estimate of 5% was used in the model on the basis of clinical expert opinion. These patients received only non-surgical infection management and did not undergo, or accrue the costs of, extraction surgery. Of the 95% of patients undergoing device extraction, 95% were assumed to have had complete extraction[15]. This was validated by clinical expert opinion. Of these, 80% were assumed to receive re-implantation, and the remaining 20% were not re-implanted. Of the 5% assumed to experience an incomplete extraction of the device, we assumed no replacement device was required. These inputs were based on clinical expert opinion.

Mortality

Among patients with a major CIED infection, mortality within the first 12 months was assumed not to differ between patients who received a replacement device and those who did not; however, life expectancy for those who survived to 12 months was assumed to differ between these patients. The mortality rates for patients without a CIED infection and patients who experience a complete extraction following a CIED infection were obtained from the Shariff *et al.*[12] study. Mortality rates in patients who experienced a partial extraction or in whom extraction was not undertaken were assumed to be double the rate associated with a complete extraction[16]. The probabilities of death at 12 months used in the decision tree were: no infection = 0.064; complete extraction = 0.211; partial/no extraction = 0.422.

Costs and resource use

Antibiotic costs: Patients in the TYRX arm were assumed to receive the Envelope at a one-off cost of £719.00 (prices in 2015 GBP). In addition to the antibiotics eluted by the Envelope (minocycline and rifampicin) all patients who received a TYRX Envelope in the Shariff *et al.*[12] study received additional prophylactic antibiotics. In the absence of detailed information on the antibiotics used, usage was assumed to be equivalent to that in patients who did not receive the Envelope. Patients in both treatment arms, hence, incurred the cost of one course of prophylactic antibiotics. The mix and costs of antibiotics used are presented in the Supplementary material.

Infection and adverse event costs: The total number of cardiac ward bed days and ICU bed days for patients experiencing a CIED infection, and the associated cost per day, were obtained from Ahsan *et al.*[3] and adjusted to 2015 costs. As a sensitivity analysis, the cost per day in the cardiac ward was increased by 10% to assess the potential impact of additional costs including laboratory tests, GP visits, and X-rays. A proportion of patients experience a re-infection within 12 months (see Supplementary Table S11), with the proportions dependent on whether an extraction was undertaken successfully or not. Locations of care, daily costs, and length of stay for patients experiencing CIED infection are shown in the Supplementary Table S10.

Cost of device extraction and replacement: The cost of extraction surgery was assigned to all patients with an infection for whom extraction surgery was undertaken, irrespective of success. In addition, patients who received a replacement device following complete extraction were allocated the cost for replacement surgery and for the replacement device. The costs of device extraction and replacement were taken from UK tariffs and are shown in the Supplementary material.

Health-related quality-of-life

Health-related quality-of-life (HRQoL) was captured using utilities. Utility data were sourced from the National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 314 Guidance assessment report, which evaluated ICDs vs optimal pharmacological therapy (OPT) in the treatment of arrhythmias and CRT-Ds or CRT-Ps in addition to OPT vs OPT in the treatment of heart failure[17]. A baseline utility was assigned to all patients on entering the model according to the device received (0.73 for IPG and 0.70 for the other device types).

A utility decrement of 0.025 was applied to the baseline for all patients who experienced a major CIED infection, with an additional decrement of 0.0125 for patients who experienced extraction surgery. These values were based on decrements for infection (0.10) and surgery (0.05) sourced from the NICE TA 314 Guidance assessment report[17]. The values from the report were re-scaled to represent a 3-monthly decrement to align with clinical expert opinion that the HRQoL impact of infection and extraction surgery would last for 3 months. In addition, patients who experienced a re-infection

were assigned a further utility decrement equal to the decrement associated with an initial infection (0.025).

Estimation of long-term costs and benefits

An additional one-off cost was allocated to all patients who survived to 12 months to represent the expected costs over their remaining lifetime. These were sourced from the NICE TA 314 Guidance Assessment Report[17]. The allocated lifetime costs were based on initial device implanted, reflecting the different ongoing costs associated with each, for those who either do not need or who successfully receive a replacement device (i.e. nodes A and G). Those who require but do not receive a successful replacement (i.e. nodes C, E, and H) were assigned lower post-12-month costs reflecting both their lower life expectancy and the lack of ongoing upkeep of the device. These cost estimates, which include medication, device implantation, device-related complications and maintenance, hospitalization due to heart failure or arrhythmia, and transplantation, are presented in the Supplementary material.

In order to present a lifetime perspective, a one-off QALY estimate was allocated to all patients who survived to 12 months to represent the expected utility over the remaining lifetime for survivors. Mean post-12-month utility and life expectancy estimates were combined to derive the one-off QALY estimate.

Those either not requiring or successfully receiving a replacement CIED (i.e. nodes A and G) are expected to have a longer life expectancy than those requiring but not receiving a successful replacement (i.e. nodes C, E, and H). Estimates of life expectancy and utility were obtained from the economic analysis of ICDs, CRT-Ps, and CRT-Ds, in addition to OPT vs OPT alone described in NICE TA 314[17]. IPG patients were assumed to accrue the same life expectancy as CRT-P patients. One year was subtracted from the life expectancy estimates to avoid double-counting of the first-year horizon of the decision tree.

Utility estimates for CRT-D, CRT-P, and ICD were estimated from the ratio of predicted quality adjusted life years (QALYs) to predicted life-years from the base case results of the economic evaluation described in the NICE TA 314 assessment report[17]. The utility estimates for IPG patients with or without a device were identified in a literature review described in the NICE guidance 324 assessment report for patients with a single-chamber atrial or dual-chamber pacemaker, and for bradycardia patients with heart failure, respectively[18,19].

Analysis

Analyses were conducted from the perspective of the UK NHS. Results for the "high-risk" population for the four device types (CRT-D, CRT-P, IPG, and ICD) are presented below, the results for the "all-comers" population are presented in the Supplementary material. Results are also presented for a mix of device types. The proportion of patients receiving each device was sourced from the Mittal *et al.*[6] study. These data are presented in the Supplementary material.

Benefit is expressed as QALYs and the primary outcome measure from the economic model is an incremental cost-effectiveness ratio (ICER) which represents the ratio of incremental costs and incremental benefits associated with use of the Envelope compared to SOC. Key clinical outcomes of interest were the proportion of patients who survived to 12 months without experiencing an infection and with device extraction avoided (defined as complete or partial extraction). Other clinical outcomes of interest were fatalities and hospitalizations avoided.

Deterministic scenario analyses were undertaken to explore the impact of changes to individual parameters on the base case cost-effectiveness results. The scenarios that were explored included alternative treatment effects (via the use of different data sources), alterations to the device replacement rate, varying the assumption regarding the survival time for those who died during the initial 12 months, and variations to the cost of extraction surgery and in-patient care. Threshold analyses were also conducted on the baseline probability of infection.

Probabilistic sensitivity analyses (10,000 Monte Carlo simulations) were conducted to propagate the uncertainty in the individual parameters. Beta distributions were assigned to probabilities based on the number of events and the total sample (*N*). Where the number of events and total sample (*N*) were unknown, a standard error of 10% was assigned to probabilities and a beta distribution fit to these data through the method of moments. Utility values were also assigned beta distributions by adopting this approach. Costs and resource use frequencies were assigned a standard error of 10%, where a measure of uncertainty was not reported alongside the mean estimate. These were assigned gamma distributions based on the method of moments.

Results

The predicted short-term clinical outcomes arising from the modeling for the "high-risk" population are presented in Table 1. As baseline infection rates were assumed to be equivalent across device types, these clinical outcomes are independent of device type. TYRX decreased the absolute rate of CIED infection relative to SOC (−2.9%). In addition, the absolute rate of survival to 12 months without a CIED infection increased with use of TYRX relative to SOC (+2.8%). Use of TYRX was also associated with a reduced probability of

Table 1. Predicted clinical outcomes, 12-month time horizon.

Outcome	SOC	TYRX	Relative change	Number needed to treat (NNT)
Proportion without CIED infection	96.7%	99.5%	+2.9%	36
Proportion without CIED infection surviving to 12 months	90.5%	93.1%	+2.8%	40
Device extraction	3.2%	0.5%	−84.4%	37
Hospitalization	5.5%	0.9%	−83.6%	22
Mortality	7.0%	6.5%	−7.1%	200

device extraction, hospitalization, and mortality (–84.4%, –83.6%, and –7.1%, respectively). Twenty-two patients would need to be treated with TYRX to avoid one hospitalization and 37 to avoid a device explantation.

Table 2 presents cost-effectiveness results over the 12-month time horizon stratified by device type. TYRX was less costly and more effective than SOC when used in patients with an ICD or CRT-D device. For patients with an IPG or CRT-P device, TYRX was associated with an increase in cost and a modest increase in QALYs, generating ICERs of £46,548 and £21,768 per QALY gained, respectively. As the same baseline infection rate is applied across device types, the differences in ICERs across device type are driven by the differences in costs. For the mixed device analysis, TYRX was associated with no incremental cost (£0) and was more effective (+0.004 QALYs) than SOC, probably due to the high proportion of the population receiving an ICD or CRT-D device.

The results from the scenario analyses for the 12-month time horizon are presented in Table 3. TYRX remained dominant in a number of scenarios using a 12-month time horizon, and the ICER associated with TYRX was most sensitive to the choice of baseline infection rate associated with SOC.

The results from the threshold analyses are presented in Table 4. Adopting a lifetime time horizon, TYRX is less costly and more effective (dominant) than SOC in patients with a CRT-D at baseline probabilities of infection exceeding 4.52% and is no longer cost-effective at a £30,000 threshold at a baseline probability below 1.65%. Similarly, TYRX dominates SOC in patients with CRT-P, IPG, and ICD devices at baseline probabilities of infection exceeding 5.71%, 7.69%, and 4.35% for each device, respectively. TYRX becomes cost-ineffective at a willingness-to-pay threshold exceeding £30,000, with probabilities of infection below 1.95%, 1.87%, and 1.38% for each device, respectively.

Table 2. Cost-effectiveness results (12-month time horizon).

	SOC	TYRX	Incremental
IPG			
Costs at 12 months	£1,127	£1,324	£197
QALYs at 12 months	0.68	0.68	0.004
ICER		£46,548 per QALY gained	
ICD			
Costs at 12 months	£1,420	£1,371	–£48
QALYs at 12 months	0.65	0.65	0.004
ICER		Dominant	
CRT-P			
Costs at 12 months	£1,256	£1,345	£89
QALYs at 12 months	0.65	0.65	0.004
ICER		£21,768 per QALY gained	
CRT-D			
Costs at 12 months	£1,518	£1,387	–£130
QALYs at 12 months	0.65	0.65	0.004
ICER		Dominant	
Mix of device types			
Costs at 12 months	£1,362	£1,362	£0
QALYs at 12 months	0.66	0.66	0.0004
ICER		£7 per QALY gained	

Discussion

Precise estimates of incidence of CIED infections in the UK are lacking. However, the number of device implant procedures is increasing. The increasing number of procedures means that the observed infection rate is likely to rise, with an associated burden both on patients and on healthcare resource use in the UK NHS[1].

The study reported here represents the first attempt to quantify the lifetime impact of using a TYRX Absorbable Antibacterial Envelope, in addition to standard infection control protocols, on healthcare resource use, costs, and patient-centred outcomes. Particular emphasis was placed on the sub-group of CIED patients who would conventionally be considered at "high-risk" of infection. In our modeling, 3.2% of "high-risk" patients receiving SOC infection prophylaxis were predicted to require a CIED extraction procedure (partial or complete) within the first year of usage, and 5.5% were predicted to be hospitalized due to re-infection or device extraction within the first 12 months. In all, 90.5% of "high-risk" patients using SOC were estimated not to experience a CIED infection and to survive to 12 months.

Patients using TYRX, in addition to SOC, were predicted to have a decreased likelihood of experiencing a CIED infection and a reduction in the probability of experiencing either a CIED extraction procedure or a hospitalization within

Table 4. Threshold analysis on baseline probability of infection.

Scenario	CRT-D	CRT-P	IPG	ICD
TYRX dominates SOC	4.52%	5.71%	7.69%	4.35%
TYRX cost-effective at a £20,000 threshold	2.09%	2.50%	2.50%	1.79%
TYRX cost-effective at a £30,000 threshold	1.65%	1.95%	1.87%	1.38%

Table 3. Scenario analyses by device (12-month time horizon).

Scenario	CRT-D	CRT-P	IPG	ICD
Base case (TYRX vs SOC)	Dominant	£21,768	£46,548	Dominant
Alternative source for baseline infection rate[5]	£55,497	£109,167	£131,058	£75,535
Alternative source for baseline infection rate[3]	Dominant	Dominant	£14,132	Dominant
Alternative source for baseline infection rate[4]	Dominant	£6,353	£31,642	Dominant
Alternative source for baseline infection rate[7]	Dominant	Dominant	Dominant	Dominant
Exclude societal costs	Dominant	£21,955	£46,728	Dominant
Reduce device replacement rate to 50%[a]	£1,991	£35,534	£50,297	£14,515
Increase device replacement rate to 100%[a]	Dominant	£12,591	£44,049	Dominant
Assign QALYs to patients who die in last 3 months	Dominant	£26,670	£57,184	Dominant
Assign QALYs to patients who die immediately	Dominant	£34,422	£74,118	Dominant
Increase device specific extraction surgery costs by 10%	Dominant	£20,267	£45,096	Dominant
Increase cost of inpatient care by 10%	Dominant	£12,004	£37,106	Dominant

[a]For patients who have had a complete extraction following a CIED infection.

12 months of initial device implantation. These benefits were ultimately driven by the derived infection relative risk estimate for TYRX compared to SOC (0.163). Such reductions would have a positive impact on clinical practice.

At cost-effectiveness thresholds conventionally used in UK device-related reimbursement decisions (between £20,000–£30,000 per QALY gained)[16,20–22], TYRX represents good value for money. At a 12-month time horizon, TYRX was also less costly and more effective than SOC in patients with a CRT-D or ICD device.

A range of scenario/sensitivity analyses were undertaken, and the model was shown to be generally robust to all changes. The exception to this was the choice of source for the baseline infection rate, where alternative sources resulted in some instances where TYRX was cost-saving (the dominant option) and others where the ICER increased beyond £20,000 per QALY gained. The threshold analyses indicated that TYRX dominated SOC at baseline probabilities of infection exceeding 7.69% for all device types, whereas TYRX would be considered cost-effective at a willingness-to-pay threshold of £30,000 when used in any device at a baseline probability of infection exceeding 1.95%. No ICERs in excess of £30,000 per QALY gained were generated by the scenario analyses when using a lifetime time horizon and TYRX remained the dominant comparator in a number of scenarios when a 12-month time horizon was adopted.

One of the limitations of the current model is the absence of device-specific data for infection rates and mortality rates. Moreover, the current model is informed by data reported in observational studies due to the lack of prospective randomized trials in this disease area. The WRAP-IT[8] or ENVELOPE study[9] may provide these data to populate the model. It was necessary to make a number of assumptions in the model including those around the proportion of patients experiencing a successful/partial extraction and device replacement following infection, baseline infection rates across device types, the use of antibiotics in those receiving TYRX, and the impact of infection on the utility of the patient. The results of the sensitivity analyses, however, indicate that the model is robust to changes in these assumptions.

Overall, our study findings, based on current knowledge and evidence available, suggest that TYRX is a cost-effective treatment option for reducing post-surgical infection risk when used in conjunction with all CIEDs.

Transparency

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