National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

TYRX Absorbable Antibacterial Envelope for preventing infection from cardiac implantable electronic devices

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	NHS England Cardiac Services CRG	Appropriate as it is in use in some organisations.	Thank you for your comment.
	Medtronic	Yes, it is appropriate to refer this topic. The topic is highly relevant and timely as the prevention of infection remains a key priority for the NHS, as set out in Five Year Forward View (NHS England, 2014). Reducing health-care associated infections is high on the government's safety agenda and has recently been a subject for debate in the House of Commons (May 2018; Raising standards of infection prevention and control in the NHS (https://researchbriefings.parliament.uk/ResearchBriefing/Summary/CDP-2018-0116) Healthcare infections incur significant costs for the NHS and can cause significant morbidity to those infected. It is estimated that 300,000 patients a year in England acquire a healthcare-associated infection (NICE Quality Standard on Infection Prevention and Control QS61, 2014), with surgical site	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		infections accounting for up to 16% of all healthcare-associated infections (NICE Quality Standard on Surgical Site Infection QS49, 2013). Infections result in additional use of NHS resources and a decrease in patient safety, therefore infection reduction and control solutions are imperative in the NHS. The TYRX Absorbable Antibacterial Envelope for infection prevention with cardiac implantable electronic devices (CIEDs) is a clinically and cost-effective therapy that can help to address this issue.	
	British Cardiovascular Society	It is appropriate that NICE considers this for an appraisal.	Thank you for your comment.
	British Society for Heart Failure	This is an appropriate technology for an HTA.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	The number of device implant procedures is increasing, the rate of infection is also increasing, therefore it is appropriate to refer this topic to NICE.	Thank you for your comment.
Wording	NHS England Cardiac Services CRG	Yes, from a lay perspective the wording appears to reflect the issues very clearly.	Thank you for your comment.
	Medtronic	TYRX is indicated for pacemakers and implantable defibrillators, which includes cardiac resynchronisation therapy devices. We therefore recommend that the following term is used to provide clarity that all types of device are in scope: ‘cardiac implantable electronic device (CIED)’. This also	Thank you for your comment. The wording of the title and population has been amended to ensure all

Section	Consultee/ Commentator	Comments [sic]	Action
		reflects the terminology used in the Topic Briefing document. As such, would be appropriate to amend the draft remit wording as follows: *"To appraise the clinical and cost effectiveness of TYRX within its CE mark for preventing infection following cardiac implantable electronic device (CIED) implantation or replacement."*	relevant devices are captured.
	British Cardiovascular Society	The purpose of the product is to reduce CIED-related infection. I would recommend that the cost-effectiveness analysis needs to include the costs associated with CIED infection, primarily around extraction, rather than just using QALY.	Thank you for your comment.
	British Society for Heart Failure	Appropriate wording.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	The wording is appropriate.	Thank you for your comment.
Timing Issues	NHS England Cardiac Services CRG	Not urgent but routine. However, these pouches are relatively expensive so if not evidenced to be of benefit may reflect a cost saving to the NHS. If beneficial, will induce a cost impact.	Thank you for your comment.
	Medtronic	TYRX is CE marked for CIEDs and is currently being used across the NHS. Data from the WRAP-IT study, an RCT that will provide key inputs to the appraisal, are expected to be available in January 2019. Timely NICE recommendations based on the WRAP-IT data will be welcomed by clinicians to help guide the use of this technology in CIED infection prevention.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Cardiovascular Society	Not urgent.	Thank you for your comment.
	British Society for Heart Failure	Not urgent.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	The burden of device infection is significant for the NHS, therefore addressing this issue requires immediate attention.	Thank you for your comment.
Additional comments on the draft remit	NHS England Cardiac Services CRG	None.	
	Medtronic	None.	
	British Cardiovascular Society	None.	
	British Society for Heart Failure	None.	
	British Association for Nursing in	None.	

Section	Consultee/ Commentator	Comments [sic]	Action
	Cardiovascular Care		

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NHS England Cardiac Services CRG	Yes.	Thank you for your comment.
	Medtronic	There are a few areas within the Background section that we feel would benefit from additional clarification or information. We have noted these as follows: • Only Pacemakers and ICDs have been described. Cardiac resynchronisation therapy (CRT) with defibrillator (CRT‑D) or CRT with pacing (CRT‑P) should also be described for completeness. A short description following the first sentence on pacemakers and ICDs as follows would be helpful i.e. *"Cardiac resynchronisation therapy (CRT) with defibrillator (CRT‑D) or CRT with pacing (CRT‑P) are used a treatment option for left ventricular dysfunction in people with heart failure where medical therapy is no longer working."* • Where the number of CIEDs are stated, it may be helpful to include the specific CRT device figures. • Where "pacing devices" is stated, this should be replaced with "*CIEDs*" for consistency of terminology and to reinforce that all types of cardiac devices are in scope.	Thank you for your comment. The wording of the title and population has been amended to ensure all relevant devices are captured. Comment noted. The rate of infections had

Section	Consultee/ Commentator	Comments [sic]	Action
		• In line 6, the infection rate that is presented (3-4%) reflects the rate reported by investigators in the literature for patients at high risk of infection. Device infection occurs in 1–2% of CIED recipients overall, and in 3–4% of high-risk patients. In line with the draft remit that includes all CIED patients ('all-comers'), a rate of 1-4% is more accurate. We recommend that this sentence is amended as follows: *"It is estimated that 1-4% of all CIED patients will develop a CIED infection".* • In line 7, reference is made only to 'surgical site infection'. For completeness and accuracy we would recommend that the term "*CIED infection"* is used here and throughout the appraisal to replace surgical site infection. CIED infection includes surgical site infection in addition to other potential infections arising from CIED implantation.	been updated in the scope
	British Cardiovascular Society	The 3-4% estimate of infection risk is not universal and to a large extent is based on US data, where the infection rate is significantly higher than in the UK. The infection rate in many UK centres is □1% and this is similar to the data in some of the TYRX literature (Mittal S et al Heart Rhythm 2014; 11:595-601). MADIT-CRT showed a CRT-D infection rate of 1.1% and an ICD infection rate of 0.7%. There is no universal definition of CIED infection nor the time scale over which this should be evaluated. Infection can take over 12 months to become apparent. In the TYRX trials this timescale may be as low as a mean of 1.9 months, which is inappropriate. The data on TYRX is all US based. There is no European data. There is no published randomised trial.	Thank you for your comment. Comment noted. The rate of infections had been updated in the scope

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Heart Failure	The main issue is that the rate of device infection is not known precisely. Does infection only mean that requiring device explantation, or include even superficial infection that resolves with oral antibiotics?	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	Portrays accurate information. The true rate of infection is probably higher due to the difficulty in diagnosing infection related to devices. The burden is likely to be higher than data suggests. Not all infected patients may represent to cardiology, therefore that data may not be captured.	Thank you for your comment.
The technology/ intervention	NHS England Cardiac Services CRG	Yes.	Thank you for your comment.
	Medtronic	Yes.	Thank you for your comment.
	British Cardiovascular Society	Yes.	Thank you for your comment.
	British Society for Heart Failure	Yes.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	Accurately decribes the technology.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	NHS England Cardiac Services CRG	Yes see comments.	Thank you for your comment.
	Medtronic	We recommend that the wording should be amended to: **"*People requiring a cardiac implantable electronic device (CIED), including replacements.*"**	Thank you for your comment. The wording of the title and population has been amended to ensure all relevant devices are captured.
	British Cardiovascular Society	Although the overall population is defined appropriately, it is unrealistic that this product should be considered for all patients undergoing CIED implant or revision, both in terms of benefit and cost-effectiveness. The technology should be reserved for patients at high risk of infection (as defined in the literature).	Thank you for your comment. High risk patients have been included as a subgroup
	British Society for Heart Failure	Appropriately. The main groups to consider are new implants, generator changes, high risk patients.	Thank you for your comment. High risk patients have been included as a subgroup
	British Association for Nursing in Cardiovascular Care	The population should also include people requiring pacemakers or defibrillators for treatment of heart failure as well as arrhythmias. Subcutaneous ICD are lower risk of infection therefore should not be included in this group	Thank you for your comment. The population has been amended.

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	NHS England Cardiac Services CRG	No comparator.	Thank you for your comment. Consultees at the workshop advised that the Collatamp device (collagen matrix impreganated with gentamicin) may be used to cover the CIED to prevent infection. This has been included as a comparator in the final scope
	Medtronic	Yes. Pre-operative intravenous antimicrobial prophylaxis is the current standard of care for infection prevention.	Thank you for your comment. Collatamp is also included as a comparator (see above)
	British Cardiovascular Society	In terms of a comparator, this should be patients receiving pre-operative intravenous antibiotics in line with the BSAC joint working party recommendations.	Thank you for your comment. Collatamp is also included as a comparator (see above)
	British Society for Heart Failure	Pre-operative antibiotics alone (although antibiotic regimes vary greatly across the world).	Thank you for your comment. Collatamp is also included as a comparator (see above)

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	NHS England Cardiac Services CRG	See comments.	Thank you for your comment.
	Medtronic	Yes. Infection avoidance is a key outcome measure. Infection is described in the draft Scope as *'device-related surgical site infection'*, however we strongly advise that this outcome measure is amended to the broader term "*CIED infection*". This ensures that all relevant types of infection can be considered including surgical site infection and is line with the definition provided in the 'Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection' by Sandoe et al. (2014). It also reflects the primary outcome measure in the ongoing landmark RCT WRAP-IT study on TYRX (Tarakji et al., Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) Design paper, Am Heart J 2016;180:12-21), where CIED infections are defined as: (1) superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion, or purulent drainage, (2) deep incisional or organ/space (generator pocket) surgical site infection (SSI) that meet the Centers for Disease Control and Prevention (CDC) criteria, independent of time from surgery, (3) persistent bacteremia, or (4) endocarditis (resulting from lead infection). Device migration is not currently included as an outcome, however we recommend that this should be included in the Scope as a relevant outcome measure given that TYRX provides stabilisation of the device and helps prevent migration.	Thank you for your comment. Consultees noted that device related infection is preferred to surgical site infection (which implies that the infection can be superficial). The final scope has been updated. Consultees noted that device migration was not a relevant outcome as the focus of the appraisal is the reduction of device related infections.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Cardiovascular Society	The outcome measure has to be CIED-related infections requiring re-intervention. Other measures are not relevant.	Thank you for your comment.
	British Society for Heart Failure	Yes. However, as far as I can see, the only TYRX studies have used historical controls and not part of a RCT.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	No consensus on standard care is currently established. Establishing standards for prophylaxis antibiotic therapy is required. Need to specifically assess psychological effects. Not all infected patients may represented to cardiology, therefore the data on infections may underestimate the rate. (Sandoe et al 2015)	Thank you for your comment. Consultees at the workshop were in agreement that pre-operative intravenous antimicrobial prophylaxis is the current standard of care for infection prevention.
Economic analysis	NHS England Cardiac Services CRG	Difficult to assess.	Thank you for your comment.
	Medtronic	The impact of TYRX following CIED implantation is relatively short-term, and CIED infection typically occurs within one-year post-implant, therefore a 12-month time horizon would be expected to capture the key costs and benefits of the therapy. A life-time horizon should also be considered alongside this to ensure that any differences in lifetime costs and benefits due to mortality differences are accounted for.	Thank you for your comment. Consultees at the workshop also noted that staph. Epidermis infections can take longer than 12 months to develop. The company agreed to take this into consideration in

Section	Consultee/ Commentator	Comments [sic]	Action
			the economic modelling.
	British Cardiovascular Society	Measuring cost-effectiveness solely in terms of QALYs is not appropriate. The main cost to the NHS (and patient) is infection and re-intervention; therefore, the cost-effectiveness needs to consider the costs of treating CIED-related infection. Furthermore, CIED infections, particularly Staph. epidermidis can take more than one year to develop, therefore, data analysis within this time period e.g. COMMAND, needs to be carefully considered in this regard. Cost to the NHS for CIED related infections is primarily related to extraction / hospital stay. Ahsan et al (Europace, 2014) estimated this cost as approximately £31,000 per patient.	Thank you for your comment. The appraisal will consider the differences in cost and the length and quality of life with TYRX compared with standard care.
	British Society for Heart Failure	Seems fair.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	Will Tyrx puches be supplied at zero cost via NHS supply chain? This will impact on the economic analysis.	Thank you for your comment. The appraisal will consider the cost and QALYs with TYRX compared with standard care.
Equality and Diversity	NHS England Cardiac Services CRG	Ok.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	Medtronic	No areas of concern.	Thank you for your comment.
	British Cardiovascular Society	No concerns.	Thank you for your comment.
	British Society for Heart Failure	No issue seend.	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	None.	
Other considerations	NHS England Cardiac Services CRG	See comments.	Thank you for your comment.
	Medtronic	None.	
	British Cardiovascular Society	Please see under “Questions for Consultation.”	Thank you for your comment.
	British Society for Heart Failure	What equates to a “High risk” individual is reasonably well recognised. This is a group where this device *may* be cost effective	Thank you for your comment. Consultees at the workshop heard the results of the

Section	Consultee/ Commentator	Comments [sic]	Action
			WRAP-IT study will be used to define 'high risk' of infection.
	British Association for Nursing in Cardiovascular Care	None	
Innovation	NHS England Cardiac Services CRG	Yes.	Thank you for your comment.
	Medtronic	We believe TYRX is an innovative technology as it is the first and only antibacterial envelope available that has been shown to reduce or prevent CIED infection. With current standard of care in patients undergoing CIED implantation or replacement there is a 1-4% risk of infection. This infection risk can be reduced or eliminated with use of TYRX therefore this represents a novel technology that can improve patient safety and quality of life whilst reducing NHS resources.	Thank you for your comment.
	British Cardiovascular Society	This is a 'step-change' in management. There are other products available that perform a similar function e.g. Collatamp. In terms of calculating the cost-effectiveness, the Committee should access NICOR data to look at UK re-intervention rates for devices and implant / generator procedures rather than be reliant on US dominated literature. Furthermore, as stated above, the Committee needs to focus on the cost of re-intervention (extraction) rather than simply QALYs.	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Heart Failure	Innovative, but seems very costly (more expensive than a pacemaker!).	Thank you for your comment.
	British Association for Nursing in Cardiovascular Care	Research does not appear to explore the burden & impact on petients who experience device infection. Anxiety & depression is already understood to be higher in cardiac patients and even more so in ICD recipients. If those patients then experience and infection this could significantly impact on their quality of life and have a hige impact on their psychological wellbeing.	Thank you for your comment.
Questions for consultation	NHS England Cardiac Services CRG	See comments.	Thank you for your comment.
	Medtronic	**How should surgical site infection be defined?** As per our above comment, we believe that it is more appropriate to use 'CIED infection' as an outcome and have provided the definition. **How should high risk of infection be defined?** There are limited risk scoring systems in place to assess patient risk for CIED infection, however the following procedural and patient risk factors have been shown to play a significant role: • Early re-intervention; • CRT-D or ICD implants (heavier device); • 2 or more leads in place (longer procedure); • Device replacement or revision; • Patient characteristics including but not limited to: -Corticosteroids use;	Thank you for your comment. The wording of the title and population has been amended to ensure all relevant devices are captured. Surgical site infection has been replaced with device related infection. Consultees at the workshop heard the results of the WRAP-IT study will be used to

Section	Consultee/ Commentator	Comments [sic]	Action
		-Renal insufficiency and failure; -Diabetes. We anticipate that the WRAP-IT study will provide further data to more clearly profile and define the high-risk population. **Do all patients receiving a pacemaker or defibrillator have it inserted within a pouch?** No, this is not standard of care. Approximately 70 centres across are currently using TYRX, either with selected high-risk patients or in all CIED patients (all-comers). TYRX is being used in approximately 20% of Medtronic CIED replacements. There are also alternative pouches on the market, with the primary aim of preventing device migration rather than to prevent infection. To our knowledge these are being used in only a very small number of implants. **What is the current antibiotic prophylaxis regimen for patients having a pacing device without TYRX?** All patients undergoing CIED implantation typically receive prophylactic antibiotic treatment as standard of care as per current UK Guidelines outlined in this Scope. Patients are not stratified by infection risk. Patients receiving TYRX also receive the standard of care prophylaxis. **Are there any subgroups of people in whom TYRX is expected to be more clinically effective and cost effective or other groups that should be examined separately?** The use of TYRX in CIED patients at high risk of infection should be a key area of focus. The absolute event rates in the case-matched control groups	define 'high risk' of infection. Consultees at the workshop agreed that as the focus of the scope is the prevention of CIED related infection pouches that are not impregnated with antibiotics are not a relevant comparator. Collatamp (a collagen material impregnated with gentamicin) can be used to wrap around CIED's when they are implanted and has therefore been included as a comparator.

Section	Consultee/ Commentator	Comments [sic]	Action
		across various TYRX studies show higher rates of CIED infection in selected patient populations: a rate of 4.3% was reported by Kolek (2013) and a rate of 3.6% was reported by Mittal (2014). In the prospective analysis by Kolek and colleagues (2013), use of TYRX in 'high-risk' patients was associated with a reduction in CIED infections when compared to a matched control cohort. The decreased likelihood of experiencing a CIED infection in high-risk patients with TYRX compared with standard management is predicted to result in a reduction in CIED extractions and/or hospitalisations, making TYRX less costly and more effective than standard management in this population (Kay et al., 2018). Koleck et al.. PACE 2013; 36:354–361. Mittal et al. Heart Rhythm. 2014; 11(4):595-601. Kay et al. J Med Econ. 2018 Mar;21(3):294-300. **Where do you consider TYRX will fit into the existing NICE Pathways, heart rhythm conditions and chronic heart failure?** As an adjunctive therapy, uptake of TYRX will not require any modification of the existing patient pathways.	
	British Cardiovascular Society	**1. How should a surgical site infection be defined?** For the purposes of this TA, this should be primarily pocket infection or evidence of systemic infection e.g. endocarditis. It should not include local redness of the skin but could include superficial infection *that requires re-intervention*.	Thank you for your comment. See the above response for changes to the final scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		2. How should high risk of infection requiring a pacemaker or defibrillator be defined? High risk patient factors are defined in the HRS 2017 consensus document and include: diabetes, renal disease, advanced age, chronic obstructive pulmonary disease, corticosteroid use, history of previous device infection, malignancy, heart failure, anticoagulant drug use and skin disorders. High risk procedure factors include: any reopening of the pocket, including generator change, CIED upgrade, device replacement/revision; temporary pacing and operator inexperience **3. Do all patients receiving a pacemaker or defibrillator have it inserted within a pouch?** Using this product to act as an anchor is unnecessary. All CIEDs have an eyehole to enable the device to be sutured in place to fascia or other tissue. It is not recommended that all patients should receive an antibiotic impregnated pouch, only those at particularly high risk (would require a number of factors described in question 2). **4. Are alternative 'pouches' used in the placement of pacing devices?** Alternative pouches include the Parsonnet Pouch (Bard) and CanGaroo ECM Pouch (CorMatrix). Alternative antibiotic delivery systems include Collatamp G (EUSA Pharma) **5. What is the current antibiotic prophylaxis regimen for patients having a pacing device without TYRX? Are patients at high risk of a surgical site infection treated? Would the antibiotic prophylaxis regimen be different for patients having TRYX?** The current recommendations are to use a cephalosporin or teicoplanin intravenously prior to the procedure (BSAC guidelines). This would be no	

Section	Consultee/ Commentator	Comments [sic]	Action
		different for patients receiving TYRX as there is no evidence to suggest that the i.v. antibiotics can be omitted. **6. Are the outcomes listed appropriate? Should outcome related to device migration be included (for example lead displacement)?** Covered above. The main outcome measure is device re-intervention due to infection. Device migration is not relevant as it is not specific to this product (v.s.) and is impossible to quantify. Lead displacement is not an appropriate outcome measure. **7. Are there any subgroups of people in whom TYRX is expected to be more clinically effective and cost effective or other groups that should be examined separately? Should people who are having a replacement of a cardiac implantable electronic device be included as a subgroup?** Sub-group analysis will be difficult as the numbers will be very small. As stated in question 2, this product should be used in patients at high risk e.g. 2 or more risk factors. **8. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** The main factor that will be a barrier to adoption of the technology is cost. Use of TYRX in a patient undergoing a single chamber pacemaker implant will double the cost of the procedure and as all costs are covered by tariff, this will make such a procedure a financial loss to the hospital. With the introduction of zero cost procurement, this will also apply to other procedures such as ICDs and CRT devices.	
	British Society for Heart Failure	None	

Section	Consultee/ Commentator	Comments [sic]	Action
	British Association for Nursing in Cardiovascular Care	How will Tyrx pouches be supplied via supply chain – what cost? Current evidence does not acknowledge that many patients may have infections not treated by cardiology and therefore not recorded as device infections. If national figures do not represent the actual number then the potential benefit in reduction of infections could be higher. Current research does not appropriately measure the impact of infection on the individual patients, psychogical, quality or life, financial burden. Anecdotally patients experience a sigficant deterioration in their quality of life and the impact on their psychological wellbeing.	Thank you for your comment.
Additional comments on the draft scope	NHS England Cardiac Services CRG	The heterogeneity of antibiotic regimens in use would make it difficult to discern the attributable benefit of TYRX but it is a question worth asking. How should an infection be defined – is it simply erythema (and if so at what stage), inflammation requiring antibiotics only or inflammation requiring re-intervention surgically? It may be wise to assess the impact of TYRX in patients at high risk of infection as defined in the scope and separately in generator change or upgrade procedures. Not all patients receive a pouch It is not relevant to assess other complications such as lead displacement as these other complications are determined in the main by technical expertise not offset by use of a pouch.	Thank you for your comment.
	Medtronic	We thank NICE for the opportunity to comment on this topic and have no further comments on the scope.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Cardiovascular Society	Limitations of presented data: • No clear definition of CIED infection • No data from RCT • Majority of data if from a technology that is not the product seeking approval i.e. from a non-biodegradable product • All data is US based where complication rates differ to UK practice • No clear definition of what constitutes high risk • Studies not blinded so operator may well be taking more care when using the product as they are aware it is high risk procedure • Experience of operators not mentioned	Thank you for your comment.
	British Society for Heart Failure	None.	
	British Association for Nursing in Cardiovascular Care	None.	

Comment 3: provisional matrix of consultees and commentators

Section	Consultee/ Commentator	Comments [sic]	Action
Provisional matrix of consultees and commentators	NHS England Cardiac Services CRG	None.	
	Medtronic	It would be appropriate and important to include the following organisations to the list of consultees: • Sepsis Trust • British Society for Antimicrobial Chemotherapy (authors of the Diagnosis, Prevention and Management of CIED's Guidelines, Sandoe et al. 2015) • Nursing Officer for Communicable Diseases, Department of Health	Thank you for your comment. They have been added to the matrix.
	British Cardiovascular Society	I would recommend including as consultees the British Society for Antimicrobial Chemotherapy who were the host organisation for a report on prevention of CIED infection (J Antimicrob Chemother 2015; 70: 325-359) which considered the use of TYRX.	Thank you for your comment. They have been added to the matrix.
	British Society for Heart Failure	None.	

Comment 4: regulatory issues

Section	Consultee/ Commentator	Comments [sic]	Action
Remit	Does the wording of the remit reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.	For accuracy the draft remit wording could therefore be modified to: *"To appraise the clinical and cost effectiveness of TYRX within its CE mark for preventing infection following cardiac implantable electronic device (CIED) implantation or replacement."*	Thank you for your comment, this has been amended.
Current or proposed marketing authorisation	What are the current indications for the technology?	Cardiac implantable electronic devices (CIED).	Thank you for your comment.
	What are the planned indications for the technology?	Neurostimulator implantable pulse generators including Deep Brain Stimulation (DBS), Spinal Cord Stimulation (SCS), and Sacral Nerve Stimulation (SNS).	Thank you for your comment.
	Which regulatory process are you following?	CE Marking	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	What is the target date (mm/yyyy) for regulatory submission?	Submitted September 2015, with updated submission in March 2017.	Thank you for your comment.
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable)	N/A	
	What is the anticipated date (mm/yyyy) of regulatory approval?	November 2018	Thank you for your comment.
	What is the anticipated date (mm/yyyy) of UK launch?	TYRX is already being used for CIEDs in the UK NHS. For neurostimulator implants the UK launch date is to be confirmed pending CE marking approval.	Thank you for your comment.
	Please indicate whether the information you provide concerning the proposed	N/A - TYRX for neurostimulation implants is not in Scope.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.		
Economic model software	NICE accepts executable economic models using standard software, that is, Excel , DATA, R or WinBUGs. Please indicate which software will be used. If you plan to submit a model in a non-standard package, NICE, in association with the ERG,	The current economic model has been constructed using Microsoft Excel. It is anticipated that any updates to the model will be made on Excel.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non –standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software		

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

N/A