

World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) NCT02277990

- Clinical Investigation Plan, version 1.0 29JUL2014
- Statistical Analysis Plan, version 1.0, 21JUL2015
 - Statistical Analysis Plan Amendment #1, version 1.0, 05JAN2018
 - Statistical Analysis Plan Amendment #2, version 1.0, 10JUL2018
 - Final Statistical Analysis Plan, version 1.0 + Amendments, 31JUL2018



Medtronic

**World-wide Randomized
Antibiotic Envelope
Infection Prevention Trial
(WRAP-IT)**

Clinical Investigation Plan

Version 1.0

29JUL2014

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LISTING OF ABBREVIATIONS

AE	Adverse Event
ASEAN	Association of Southeast Asian Nations
CDC	Centers for Disease Control and Prevention
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence Interval
CIED	Cardiovascular Implantable Electronic Devices
CIP	Clinical Investigation Plan
CoNS	Coagulase-Negative Staphylococci
CRDM	Cardiac Rhythm Disease Management
CRMD	Cardiac Rhythm Management Device
CRO	Clinical Research Organization
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRT-P	Cardiac Resynchronization Therapy Pacemaker
CTA	Clinical Trial Agreement
DM	Data Management
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EC	Ethics Committee
EGM	Electrogram
EMEA	Europe, the Middle East and Africa
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HV	High Voltage
ICD	Implantable Cardioverter-Defibrillator
ICH	International Conference on Harmonization
IE	Indeterminate Event
IFL	Instructions For Use, Label
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ITT	Intent to Treat
LIA	Lead Integrity Alert
LNA	Lead Noise Alert
LSE	Lead System Event

LV	Left Ventricular
LVAD	Left Ventricular Assist Device
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NIS	Nationwide Inpatient Sample
NLE	Non-Lead System Event
PI	Principal Investigator
PIC	Patient Informed Consent
PHI	Protected Health Information
RA	Right Atrial
RV	Right Ventricular
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SIC	Short Interval Count
SSI	Surgical Site Infection
SOC	Standard of Care

SPONSOR CONTACT INFORMATION

Medtronic contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the sites as needed.

Table 1: Study sponsor contact information

Study Sponsors and Contacts	
<i>Worldwide clinical study leader</i> Daniel Lexcen, Clinical Research Specialist Direct Phone: (+1-763)-526-9702 Direct Fax: (+1-763)-367-5904 daniel.lexcen@medtronic.com	<i>Europe, the Middle East and Africa (EMEA)</i> [Redacted]
<i>Latin America</i> [Redacted]	<i>India</i> [Redacted]
<i>Greater China</i> [Redacted]	<i>New Zealand</i> [Redacted]
<i>Association of Southeast Nations (ASEAN)</i> [Redacted]	
Study Monitors and Contacts	
<i>Worldwide monitoring leader</i> [Redacted]	<i>Monitoring leader EMEA, Greater China, ASEAN, New Zealand and India</i> [Redacted]

Name, title, address and contact number of the sponsor’s medical expert for the study:

This information may be subject to change during the course of the clinical study. Updates will be sent to the sites as needed.

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CONTRACT RESEARCH ORGANIZATIONS, ACADEMIC RESEARCH ORGANIZATIONS AND CORE LAB

Contract research organization (CRO), Academic Research Organization (ARO), and Core Lab information is provided in the table below. Additional CROs, AROs, and Core Labs may be added at a later time; contact information may be provided under separate cover.







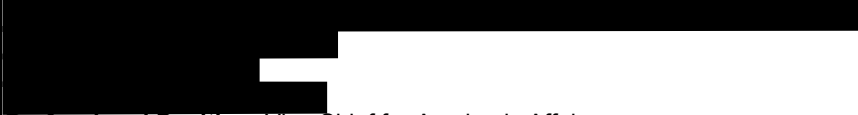
Table 2: CRO, ARO and core lab information

Contact Information	Duties performed
<i>Cognizant Technology Solutions</i> [Redacted]	<ul style="list-style-type: none">• Developments of study electronic case report forms, edit checks, and study management reports.• Review of electronic case report forms, management of discrepancies, and coding of medications and deviations.
<i>C5 Research (ARO), Cleveland Clinic</i> [Redacted]	<ul style="list-style-type: none">• Project Manager to provide a single point of contact for sponsor to communicate with the CEC team, Stats team, and CCF physicians• Assist in the education of study personnel and sites and development of study tools• Support the DMC• Coordinate CEC activities

STEERING COMMITTEE

Seven steering committee members were chosen for this study and are listed below. Additional members may be added at a later date. The steering committee members are appointed by the sponsor to assist in development and execution of this clinical study.

Table 3: Steering Committee contact information

Committee Member	Contact information
Bruce Wilkoff, MD Steering Committee Chair	 Professional Position: Director of Cardiac Pacing and Tachyarrhythmia Devices
Charles Kennergren, MD, PhD	 Professional Position: Senior Consultant, Associate Professor Department of Cardiothoracic surgery
Jeanne Poole, MD	 Professional Position: Professor of Medicine, Section Head of Electrophysiology
Ralph Corey, MD	 Professional Position: Professor of Medicine and Pathology, Gary Hock Professor of Global Health
Suneet Mittal, MD	 Professional Position: Director, Electrophysiology Laboratory; The Valley Hospital Health System; Ridgewood, NJ and New York, NY
Khalidoun Tarakji, MD, MPH	 Professional Position: Staff Electrophysiologist Section of Cardiac Pacing and Electrophysiology Heart and Vascular Institute Cleveland Clinic
Daniel Mark, MD, MPH	 Professional Position: Vice Chief for Academic Affairs Division of Cardiology, Department of Medicine; Director, Outcomes Group, Duke Clinical Research Institute

1 INTRODUCTION

1.1 Study Purpose

Medtronic, Inc. is sponsoring the **World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT)**, a randomized, prospective, multi-center, single blinded, post-market, interventional clinical study. The study has three purposes. First, the WRAP-IT study will serve as a post-approval study for those geographies requiring a post-approval study to facilitate collection of complications related to the Cardiovascular Implantable Electronic Device (CIED) procedure or system in subjects randomized to receive the TYRX™ Absorbable Antibacterial Envelope (henceforth referred to as TYRX envelope). Next, this study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, revision, or the implant of a *de novo* CRT-D. Subjects undergoing CIED generator replacement, upgrade, revision or the implant of a *de novo* CRT-D system will be randomized to either receive the TYRX envelope or not to receive the TYRX envelope. Randomization will be 1:1 and be stratified by study site and device type, high power (ICD and CRT-D) vs. low power devices (IPG and CRT-P). Finally this large device study provides the unique opportunity to prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead. These features include the lead integrity alert (LIA), lead noise alert (LNA), RV pacing impedance, and high voltage (HV) pacing impedance to detect events that affect a RV lead's pacing, sensing, or defibrillation circuit lead system events (LSE).

1.2 Study Scope

The study is expected to be conducted at up to 225 sites worldwide with up to 7,764 subjects enrolled in order to randomize approximately 6,988 subjects. Enrollment of subjects receiving a replacement low power device (i.e. IPG or CRT-P) will be capped at approximately 25% of the total randomized study population (i.e. approximately 1,746 subjects). Relative to high power device recipients, patients receiving a low power device may be at reduced risk of a major CIED infection. Thus, to ensure an adequate CIED infection event rate in the control arm, there is a desire to include a higher proportion of high power devices in the trial.

The enrollment period is expected to start in late 2014 and to take approximately 24 months. Subjects will be followed for a minimum of 12 months. Therefore, the anticipated study duration is approximately 36 months and subjects may be followed for up to 36 months depending on when they enroll in the study.

Expected participating geographies include, but are not limited to, the United States (US), Europe, the Middle East and Africa (EMEA), Greater China (Hong Kong), New Zealand, Latin America, the Association of South East Asian Nations (ASEAN) (Singapore and Malaysia), and India.

To ensure a widespread distribution of data, minimize site bias in study results and ensure that sites will be able to adequately manage and follow subjects enrolled in the study, the maximum number of randomized subjects allowed at a single site is 100 subjects. Sites are encouraged to enroll as many consecutive eligible subjects as appropriate. There is no specific minimum number of enrollments required, except where stated in the clinical trial agreement between the sponsor and the individual site.

The WRAP-IT study utilizes a group sequential design and has up to two planned analyses of the primary objective. The first analysis will occur when a minimum of 3,200 randomized subjects complete the 6-month visit and the final analysis will occur when all randomized subjects have the opportunity to complete the 12-month study visit. The study may be considered successful at the first analysis in which the primary objective is met. An independent Data Monitoring Committee (DMC) will periodically review the accumulating data and review the results of the analysis of the primary objective at each pre-specified analysis time point. Should the DMC indicate that the study is successful at the interim analysis, the study may continue to enroll and follow subjects to evaluate the effect of the TYRX envelope on CIED infections that develop post-12 months as well as collect additional follow-up in subjects with a defibrillation system in which to evaluate the lead monitoring features. However, subjects enrolled following review of the interim analysis may no longer be randomized upon recommendation of the DMC if the TYRX envelope is found to have a clear benefit.

2 BACKGROUND AND JUSTIFICATION

Over the last few decades, there has been a growing evidence of the importance of CIEDs in improving both quality of life and survival among patients with heart disease.^{1, 2} This has resulted in expansion of the indications for CIED implantation which is reflected in the most recent guidelines from the American College of Cardiology / American Heart Association/Heart Rhythm Society for CIED implantation and its most recent update.^{3, 4} With expanding indications for these devices and an increasingly aging population, more devices are implanted in older patients with more comorbidities.^{5, 6} In addition, battery depletion, evolving CIED indications (e.g., upgrades), and generator or lead advisories and recalls may necessitate one or more replacements of the device in a patient's lifetime.^{7, 8, 9} This growth of implanted CIEDs has led to an increased recognition and awareness of post-implant complications. Migration of the CIED generator from the implant site is a complication of CIED therapy that can be associated with increased morbidity and expense. Additionally, infections and lead system issues are among the most common complications, specifically post replacement.¹⁰ CIED migration, CIED infections and delayed LSE detection can create a significant resource burden on the healthcare system and can be associated with an increased risk of morbidity or mortality.^{11, 12, 13}

2.1 CIED Migration Background

Published rates of generator migration have been reported to be 0.1%-1.2%^{14, 15} Twiddler's syndrome is a form of CIED migration in which conscious or unconscious manual manipulation of the CIED by the patient leads to device migration. Importantly, recent published series of CIED implantations that utilize modern CIED generators indicate generator migration continues to occur at a clinically significant rate (1.2%)¹⁵

2.2 CIED Infection Background

2.2.1 The Rate of CIED Infection

The reported prevalence rate of CIED infection varies widely in the literature and ranges from 0.13% to above 12%.¹⁶⁻²³ This wide variation stems from the fact that most data come from retrospective series or single site registries using different definitions of CIED infections. The lack of a clear denominator and the use of different durations for follow

up have been major obstacles towards understanding of the true incidence rate of CIED infection. The Prospective Evaluation of Pacemaker Lead Endocarditis (PEOPLE) study was a multi-center prospective survey of the incidence and risk factors of CIED infections after IPG or ICD implantations 6319 patients followed for 12 months. The incidence of CIED infection was 0.56% after de-novo implantation and 0.99% for the non-de-novo procedures.²⁴ The REPLACE registry, a prospective, multi-center study collecting data about complications after device replacement (IPGs and ICDs), revealed that the 6 month infection rate was 1.4% for patients who underwent device replacement with no intent to replace leads and 1.1% for patients who underwent device replacement with planned lead addition.¹⁰ Currently, it is believed that the risk of CIED infection for primary device implantation is less than 0.5%, while for device replacement or upgrade surgeries, the risk is estimated to be between 1-5%.^{24, 25} Although the incidence of CIED infection remains low, the rate of increase in CIED infection each year is alarming. Among Medicare beneficiaries, the rate of cardiac device infections in general increased from 0.94 to 2.11 per 1000 patients between 1990 and 1999, representing a 124% increase during the study period.²⁶ Similarly the National Hospital Discharge Survey showed that between 1996 and 2003, the number of new CIED implants in the US increased by 49% (160% for ICDs vs 31% for IPGs). During the same period, the number of hospitalizations for CIED infections increased 3.1 fold (2.8 fold for IPGs and 6.0 fold for ICDs). Similarly, data from the Nationwide Inpatient Sample (NIS) discharge records between 1993 and 2008 showed that the incidence of CIED implantation increased an average of 4.7% annually, and the overall CIED implantation increased by 96%.²⁷ During the same time period, the rate of CIED infection was 1.61% representing a 210% increase.

2.2.2 Risk Factors

Several studies have identified risk factors for developing CIED infections. These include renal dysfunction,^{28, 29} heart failure,²⁸ fever within 24 hours prior to implantation,²⁴ diabetes,²⁸ oral anticoagulation use,²⁹ steroid use,³⁰ temporary pacing system at time of implant,²⁴ secondary procedures (device replacement or upgrade) as opposed to de-novo procedure^{24, 28, 29, 31, 32}, presence of more than one lead,^{30, 32} ICD implant compared to IPG,³³ abdominal implant compared to pectoral transvenous system,¹⁸ physician experience,³⁴ and early intervention for hematoma or lead dislodgement.^{22, 35} Some factors are related to the microbiology of blood stream infection as the risk of CIED infection with *Staphylococcus* bacteremia is higher than the risk with gram-negative bacilli.^{32, 35, 36} Importantly, blood stream infections increase the risk of CIED infection and, thus, risk factors for *S. aureus* blood stream infection, such as end stage renal disease requiring dialysis, may be secondarily associated with an increased risk of CIED infection.

2.2.3 Microbiology and Pathogenesis

Most infections are monomicrobial but some are polymicrobial.¹¹ Staphylococcal species are the major culprit and account for up to 80% of cases in most published series (coagulase-positive, e.g., *Staphylococcus aureus*, or coagulase-negative, e.g. *Staphylococcus epidermidis*). Almost half of these staphylococcal species are methicillin resistant.^{11, 24, 33, 36, 37, 38} Other microorganisms involved include *Corynebacterium* species *Propionibacterium acnes*, *Enterococci*, Gram-negative bacilli, fungi, anaerobes, *Candida* species and rarely mycobacteria.^{11, 38} In addition, a significant

number of patients may have negative cultures despite clear presentation of CIED infection. This is often due to poorly obtained cultures or prior antibiotic therapy.¹¹ It is believed that most infections within the first 12 months after implant are related to the initial implantation procedure or during generator change or upgrade procedures. If the generator or electrode erodes through the skin, they are by default infected, but most commonly the erosion is a manifestation of an underlying infection. Pocket infection might then spread intravascularly along the leads. Less commonly, the leads and the device pocket are infected as a result of hematogenous seeding during episodes of bacteremia.^{23,25}

2.2.4 Diagnosis

CIED infection can present as a pulse generator pocket infection, or blood stream endovascular infection, or both, with or without CIED-related endocarditis. Most patients present with pocket infection with inflammatory changes involving the device pocket itself. These changes include erythema, warmth, tenderness, drainage, and erosion through the skin with exposure of the generator or the leads.^{11,38} These local changes are sometimes accompanied by systemic signs and symptoms that include fever, chills and malaise. Other patients may present with a device pocket that looks intact but with a combination of signs and symptoms supported by blood culture findings and occasionally imaging data, especially transesophageal echo, that suggest endovascular infection involving the CIED.^{11,38,39} Patients are classified as having CIED endocarditis if they have positive echocardiographic findings and two or more positive blood cultures for typical skin organisms (coagulase-negative staphylococci, *Corynebacterium* species, *Propionobacterium* species), or one positive blood culture for all other microorganisms. Positive echocardiographic findings for CIED-related endocarditis are defined as:

1. Presence of an oscillating intracardiac mass on cardiac valve or supporting structures (in the path of regurgitant jets) or CIED leads in the absence of an alternative anatomic explanation,
or
2. Visualization of a cardiac abscess,
3. New dehiscence of prosthetic valve.

Recommendations for diagnosis of CIED infections were published in the consensus statement in 2010.²³ Despite these definitions, the diagnosis of CIED infection often represents a challenge to both the electrophysiologist and the infectious disease specialist. The challenge begins early after CIED implantation when it is important to make the distinction between CIED pocket infection and simple incisional erythema or stitch abscess, which usually responds to local measures or sometimes to a short course of oral antibiotic. Pocket hematomas can also occur after new CIED implant and are usually treated conservatively. The other challenge is often the indolent course of CIED infection (especially when the causative organism is of limited virulence, e.g., CoNS, corynebacterium, or propionobacterium) before it manifests. Pocket infection can manifest acutely but more often gradually over the course of several months or years after original implant or last pulse generator change.¹¹

2.2.5 Management

Although clinical presentation of endovascular and isolated pocket infection are quite different, the management of both types whether pocket infection or endovascular

infection involves complete system removal and antibiotic therapy. However, the type and extent of infection might affect the duration of the antibiotic therapy and the decision for the timing and strategy of re-implant.

Determining the presence of an indolent pocket infection, however, can be quite difficult. It is not rare to have erythema at the incision site during the first week of healing after device implantation. Less frequently, but still common during the first two weeks after CIED implantation, are small, superficial stitch abscesses that does not involve the pocket. This usually responds to local measures and a short course of oral antibiotics directed against staph species.^{23,25} However, when the diagnosis of CIED infection is made, complete removal of all hardware is recommended regardless whether it is a device pocket infection or endovascular infection.^{11,23,37,40} Previously published studies have shown that conservative management has an unacceptably high failure rate with higher mortality.^{24,37,38,41} Partial removal of the pulse generator and capping the lead should not be performed even in cases of pocket infection, as the relapse rate due to the retained wire is high.²³ Antimicrobial therapy is adjunctive in patients with CIED infections. Since the majority of CIED infections are caused by staphylococcal species and half of these are methicillin resistant, vancomycin may be initiated empirically after the appropriate cultures are sent. Antibiotic therapy afterwards may be tailored based on the culture and sensitivity data.

2.2.6 Financial Cost

CIED infections result in significant financial burden for patients, hospitals, and third-party payers, including prolonged hospitalization, prolonged antibacterial treatment, management of systemic complications of sepsis, and costs involved in device extraction and possible re-implantation. Over the last two decades, the in-hospital charges for CIED infection increased by almost 100%.²⁷ Among a large cohort of Medicare patients who were admitted for CIED generator implantation, replacement or revision, CIED infection increased the cost by 1.4 to 1.8 fold depending on the type of CIED. Intensive care hospitalization accounted for more than 40% of the incremental costs. Cost ratios with ICD infection appeared to be substantially higher than with IPG infection.⁴²

2.2.7 Mortality

The high mortality associated with CIED-related endocarditis has been recognized by many investigators in the past, even before the recent surge in CIED implantation. This mortality could be as high as 31-66%, if the device is not removed, and 18% with complete device removal and antibiotic therapy.^{41,43} More recently, several studies looked into the mortality after CIED infection, whether associated with endocarditis or not, with alarming results. The National Hospital Discharge Survey showed that CIED infection increased the risk of in-hospital death more than 2-fold.⁴⁴ Among 210 patients admitted with CIED infection between 1995 and 2006 to one tertiary site, in-hospital mortality was 8% and 6 months mortality was 18%.³⁷ At the Cleveland Clinic, the 1-year mortality among 412 patients with CIED infections that underwent system removal percutaneously between 2002 and 2007 was 17% and was higher among patients with endovascular infection compared to the pocket infection group (25% vs 12% respectively).¹¹ Over the last two decades, the analysis of the Nationwide Inpatient Sample (NIS) showed that the in-patient mortality associated with CIED infection averaged 4.39%; however this mortality increased from 2.91% in 1993 to 4.69% in 2008,

representing an increase of 1% per decade.²⁷ Sohail *et al.* studied admission and long term mortality in a retrospective cohort of 200,219 Medicare patients admitted for CIED generator implantation, replacement, or revision between January 2007 and December 2007. Depending on CIED type, infection was associated with significant increases in adjusted admission mortality (rate ratios ranged between 4.8% and 7.7%) and long-term mortality (rate ratios ranged between 1.6% and 2.1%) among the 5817 patients admitted with diagnosis of infection.⁴²

A retrospective review of all 416 cases of CIED infection at Mayo Clinic between 1991 and 2008 learned that the 30-day mortality was 5.5% and the 1-year mortality was 14.6%.⁴⁵ In addition, a 3-fold protective effect (HR 0.35, 95% CI 0.16 to 0.75) against 1-year mortality was found among those who underwent immediate device removal as compared to those with delayed device removal after failure of antimicrobial therapy or no device removal. International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) enrolled 2760 patients with definitive endocarditis from 61 sites in 28 countries.⁴⁶ The in-hospital and 1-year mortality of 177 diagnosed with CIED-related endocarditis was 14.7% and 23.2%, respectively. Device removal during the first index hospitalization with CIED-related endocarditis appeared to be associated with improved 1 year survival (but not in hospital mortality), and the presence of concomitant valve infection and health-care related infections were associated with worse survival. In a recent study from the Netherlands, Dr. De Bie *et al.* reviewed the cases of all patients who received an ICD or CRT-D over the last decade at one tertiary care facility.⁴⁷ The 3-year incidence of CIED infection among the 2476 patients was 2.6% and the 1-year mortality following first CIED infection was 16.9% CIED infection appeared to be associated with 1.9 fold (2.4-fold after controlling for possible confounders) increased risk of mortality compared to patients who did not experience infection.

In summary, high mortality related to CIED infections has been identified prior to the recent growth in CIED implants. Moreover, studies between 1991 and 2012 reported in-hospital and 1-year mortality, ranging from 8% to 14.7% and 14.6% to 23.3%, respectively. Immediate device removal appeared to improve survival rates. Although lower survival rates among patients with CIED infections have been challenged in some other studies⁴⁸, both acute and long-term mortality was shown to be strongly associated with CIED infections.

2.2.8 TYRX™ Non-Absorbable and Absorbable Antibacterial Envelope

The TYRX Antibacterial Envelope is designed to hold a CIED to create a stable environment when implanted in the body. The envelope is comprised of a substrate mesh coated with an absorbable tyrosine-based polymer that contains the antimicrobial agents rifampin and minocycline.

There are two TYRX Antibacterial Envelopes: partially absorbable and fully absorbable (henceforth referred to as TYRX Non-Absorbable envelope and TYRX envelope, respectively). For purposes of this study, only the TYRX Absorbable envelope will be used. The TYRX envelope was cleared for marketing in the United States on May 20, 2013, approved by Health Canada on January 15, 2013 and at the time of this protocol version CE Mark is pending. No study site related activities will occur in a geography until the TYRX envelope is commercially available, unless pre-market use for clinical trials is allowed per local regulations and law.

The TYRX envelope is made of a knitted Glycopenre II mesh substrate coated with a mixture of absorbable tyrosine-based polyarylate polymer containing the ancillary medicinal substances minocycline and rifampin, each at the same concentration.

The envelope anchors the electronic device, and provides a substrate for tissue in-growth. After implantation, the TYRX envelope anchors the implanted cardiac device and the absorbable polyarylate polymer elutes the antibiotics while the polymer is being degraded by the patient's body. The antibiotics are completely eluted in 7-10 days.

- Rifampin dose per TYRX envelope: 102 µg/cm² is released over 7 to 10 days. Rifampin is a bactericidal antimicrobial which interferes with DNA-dependent RNA polymerase activity. Rifampin has been shown to be effective against Gram-positive bacteria including *Staphylococcus aureus* (including MRSA), *Staphylococcus epidermidis*, and *Staphylococcus Lugdunensis*, and Gram-negative bacteria, such as *Haemophilus influenzae*.
- Minocycline dose per TYRX envelope: 102 µg/cm² is released over 7 to 10 days. Minocycline is a bacteriostatic antimicrobial which inhibits protein synthesis. Minocycline has been shown to be effective against Gram-positive bacteria, such as *Staphylococcus aureus* and *Streptococcus pneumoniae* and Gram-negative bacteria, such as *Escherichia coli*, *Enterobacter aerogenes*, *Haemophilus influenzae* and *Acinetobacter baumannii*.

The above antibiotic combination has been shown to reduce infection in an *in vivo* model of bacterial challenge following CIED implantation. Additionally, multiple randomized clinical trials (RCTs) have demonstrated that incorporating the combination of rifampin and minocycline into medical devices including central venous catheters, hemodialysis catheters, and external ventricular cerebrospinal fluid drainage catheters significantly reduces device-associated infections, especially those due to *S. aureus* and coagulase-negative staphylococci (CoNS).⁴⁹⁻⁵⁴ A meta-analysis of the 5 RCTs of central venous catheters demonstrated the odds ratio for developing a catheter-related bloodstream infection is 0.26 [95% CI 0.15-0.47; P<0.0001] for the catheters incorporating minocycline and rifampin, compared to those that do not. This corresponds to a 74% reduction in the risk for central venous catheter infections when the catheters incorporate minocycline and rifampin.

In contrast to the TYRX Non-Absorbable envelope, the TYRX envelope's surgical mesh substrate (Glycopenre II) is absorbable. Therefore, there is no residual mesh remaining in the tissue pocket to serve as a potential nidus of infection. The duration of use of the TYRX envelope is rate limited by the time it takes for the patient's body to absorb the Glycopenre II mesh, about 9 weeks.

2.2.8.1 Preclinical Studies of TYRX™ Absorbable Antibacterial Envelope

In *in vitro* studies, the TYRX envelope demonstrated antimicrobial activity against organisms that include methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus Lugdunensis*, *E. coli*, and *Acinetobacter baumannii*.⁵⁵ The TYRX envelope has also been shown to reduce infection in an *in vivo animal* model of bacterial challenge following surgical implantation of the CIED pulse generator (data provided by TYRX,

Inc.).⁵⁵ Nearly identical results were obtained against a similar set of pathogens with the TYRX Non-Absorbable envelope.⁸⁰

2.2.8.2 Clinical Studies of TYRX™ Non-Absorbable Antibacterial Envelope

The clinical performance of the TYRX Non-Absorbable envelope has been evaluated in the completed COMMAND (COoperative Multicenter study Monitoring a CIED ANtimicrobial Device) clinical study published in *Pacing and Clinical Electrophysiology (PACE)*.⁵⁶ The COMMAND study was a multi-center registry of patients receiving the TYRX Non-Absorbable envelope at 10 U.S. academic, community and Veterans Affairs medical sites. The primary endpoints were successful CIED implantation and CIED infection. All patients were enrolled according to an IRB-reviewed protocol. All primary clinical end-point events were adjudicated by an independent Clinical Events Committee (CEC), and no investigator or member of the CEC was a paid consultant to, or had a financial interest in, TYRX, Inc. A total of 642 consecutive CIED recipients undergoing an initial implantation or revision/replacement procedures utilizing the TYRX Non-Absorbable envelope at 10 U.S. medical sites (2 academic, 7 community, 1 Veterans Affairs) between June 2008 and June 2009 were enrolled. Of the 642 procedures, 17 following an explanation of a CIED secondary to a prior CIED infection and 1 utilizing the TYRX Non-Absorbable envelope for an off-label indication were excluded. Analyses were performed on the remaining 624 patients. The 624 eligible procedures (patient age 70+/-13 years, 32% women, 22% Black and Hispanic, 39% diabetes, 27% renal insufficiency, 35% oral anticoagulant use) utilized pacemakers (35%), ICDs (29%), and CRT-Ds (36%). Importantly, more than two-thirds (68%) of cases in the COMMAND study were revision/replacement procedures. Nearly half of the patients (49%) had at least 3 pre-defined risk factors for CIED infection. CIED implantation was successful in 621 procedures (99.5% [95%CI 98.7-99.9]). There were 3 major infections (0.48% [95%CI 0.17-1.40]) after 1.9+/-2.4 months follow-up. The infections followed one ICD revision and two CRT-D replacements. The infection rate for initial procedures was 0% [95% CI 0.01-1.82] and for revision/replacement procedures was 0.71% [95% CI 0.26-2.06]. Additionally, IPG procedures had an infection rate of 0% [95%CI 0.01-1.66] and the combined infection rate of, ICD/CRT-D procedures was 0.74 [95% CI 0.27-2.16%].

There were two adverse events attributed to the antibacterial envelope; one unsuccessful CIED implantation and one threatened erosion. Both were treated without complication. There were 11 deaths (4 noted after publication of the study results). None were attributed to the anti-bacterial envelope or the CIED procedure. In the cohort at highest risk for CIED infection, the ICD/CRT revision/replacement procedures (n=286; 1.9 +/- 2.2 months follow-up), there were 70% fewer CIED infections compared to a historical cohort of ICD/CRT replacement procedures that did not utilize the antibacterial envelope, (n=533; 2.7+/-2.8 months follow-up) published by Gould *et al.* (1.05% vs. 3.56%).⁵⁷

Presently, two large post-marketing, prospective cohort studies of the TYRX Non-Absorbable envelope in CIED replacement procedures have completed enrollment. These two studies evaluated rates of infection and mechanical complication between patients receiving the TYRX Non-Absorbable envelope and those who did not using a historical published control group and also a retrospective case-matched control group.

These studies are the Citadel (upgrade/replacement dual and single chamber ICDs – ClinicalTrials.gov NCT01043861) and Centurion (upgrade/replacement CRT-Ds and CRT-Ps – ClinicalTrials.gov NCT01043861) studies. The studies began in January 2009 and over 50 Principal Investigators from academic, community and Veterans Affairs hospitals participated as clinical research sites. A planned 3-month interim analysis demonstrated efficacy by reducing major infections relative to implants without the TYRX Non-Absorbable envelope with no significant increase in the rate of mechanical complication. As a result of this, enrollment was limited to 464 subjects for Citadel (originally planned for 2,300 subjects) and 673 subjects for Centurion (originally planned for 2,000 prospective patients and 2,000 case-matched, non-TYRX Non-Absorbable envelope patients).

The 3-month interim analysis of the first 1,000 subjects (combined analysis of 402 Citadel and 598 Centurion subjects) completing 3 months of follow up showed an incidence of 0.10 % major infections in the TYRX Non-Absorbable envelope group vs. 1.88 % for the historical published control group ($p < 0.001$) using a one-sided z-static test with significance cutoff of 0.01. The rate of CIED malfunction requiring pocket revision (0.20 %) was significantly lower with TYRX Non-Absorbable envelope, compared to the pre-specified historical published control group without TYRX Non-Absorbable envelope (1.5 %; $p = 0.003$).

At 3-months, 533-subjects in the CRT cohort (Centurion) had case matched controls. The TYRX non-absorbable cohort showed no major infections (0.00 %), which was significantly lower than the rate among the 533- case-matched control subjects who did not received the TYRX Non-Absorbable envelope (1.13 %; $p = 0.006$). The rate of overall mechanical complications was 3.8 % for the CRT/ TYRX Non-Absorbable envelope subjects (prospective cohort) compared with 4.1 % for the retrospective case-matched control cohort that did not receive the TYRX Non-Absorbable envelope ($p = 0.75$).

A second pre-specified analysis was implemented for this 1,000 patient cohort of subjects completing 6 months of follow up (combined cohort from Centurion and Citadel). During the first 6 months after implantation, there were 2 major CIED infections (0.2 %) among those patients receiving the TYRX Non-Absorbable envelope antibacterial envelope. The major infections in the TYRX Non-Absorbable envelope combined group occurred in 1 ICD (Citadel) subject and 1 CRT (Centurion) Patient. Despite longer follow-up, the incidence of major infection among the combined Centurion/Citadel cohort (TYRX Non-Absorbable envelope subjects) was significantly lower ($p < 0.001$) than the historical published control group (ICD/CRT cohorts) at 45 days and 3 months (1.88 %).^{57,58}

A 6-month pre-specified analysis of 533 Centurion-only subjects (CRT Ds and CRT Ps) identified 1 major infection for the TYRX Non-Absorbable envelope subject population (0.2 %) compared to 6 major infections among the case-matched control group (1.1 %; $p = 0.029$). There was a rate of 5.1 % mechanical complications among the TYRX Non-Absorbable envelope subjects and 4.9 for the retrospective case-matched control subjects. There was a 6-month mortality rate of 3.4 % for TYRX Non-Absorbable envelope subjects vs. 1.3 % ($p = 0.001$) for the retrospective case-matched control subjects. As a reference, the reported 6-month mortality rate in a cohort of *de novo* CRT-D device recipients from the MIRACLE ICD trial was 7.6%.⁷⁹ Therefore, it is possible that this difference in mortality rates was due to ascertainment bias created

because the control group was derived from case-matched and non-prospective medical chart reviews.

2.3

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



2.4 Study Justification

Previous case control and single arm studies suggest that the TYRX envelope may be effective at preventing CIED infection.⁷³ However, definitive evidence in the form of a randomized clinical trial regarding the effectiveness of the TYRX envelope to prevent CIED infections is lacking. Thus, the WRAP-IT study is warranted. Specifically, the WRAP-IT study will evaluate the utility of the TYRX envelope for preventing CIED infections in a large randomized single blinded study conducted in a group of subjects at high risk for CIED infection. In addition, the large size of the WRAP-IT study provides a mechanism to address the CE mark post approval requirements of the TYRX envelope as well as enables the first prospective assessment of the performance of Medtronic's lead monitoring feature set.

3 SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted using the components described in the table below. Instructions for use of the devices used in this study are provided in Appendix J and the Investigator’s Brochure (TYRX™ Absorbable Antibacterial Envelope, henceforth referred to as TYRX envelope) or their respective manuals (other system components).

Subjects meeting one or more of the following criteria may be enrolled: 1) an ACC/AHA/HRS or ESC guideline-recommended need for a *de novo* CRT-D and subject has a geography approved indication for a CRT-D, 2) an existing IPG, CRT-P, ICD, or CRT-D undergoing generator replacement or generator upgrade with or without the addition of new leads, or 3) an existing IPG, CRT-P, ICD, or CRT-D undergoing a CIED system revision (pocket or lead) procedure. Subjects who enroll in the study and proceed with a device procedure must be implanted with a Medtronic single, dual, or triple chamber pacemaker or defibrillator that has received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Any market-released, commercially available lead(s) can be used in this study.

Additional study components which may be utilized in this study for subjects include Medtronic CareLink® Monitor and CareLink® Network, and Medtronic programmers. These components are described in the following sections.

Table 4: System component information

Model Number	Component (Manufacturer)	Market-released
System Components		
CMRM6122 or CMRM6133	Medtronic TYRX™ Absorbable Antibacterial Envelope	Market Released*
Refer to Appendix P	New or previously implanted market released Medtronic IPG models which may include: Adapta, Advisa, Ensura, Relia, Revo, Sensia, Versa or any subsequently market-released Medtronic IPG	Market-released models may vary by geography
Refer to Appendix P	New or previously implanted market released Medtronic CRT-P models which may include: Consulta, Syncra, Viva XT or any subsequently market-released Medtronic CRT-P	Market-released models may vary by geography
Refer to Appendix P	New or previously implanted market released Medtronic ICD models featuring SmartShock™ Technology, which may include: Evera S, Evera XT, Protecta, Protecta XT, or any subsequently market-released Medtronic ICD	Market-released models may vary by geography
Refer to Appendix P	New or previously implanted market released Medtronic CRT- D models featuring SmartShock™ Technology, which may include: Brava, Brava Quad, Protecta, Protecta XT, Viva S, Viva S Quad, Viva XT, and Viva XT Quad, or any subsequently market-released Medtronic CRT-D	Market-released models may vary by geography

--	Any new or previously implanted market-released transvenous right ventricular (RV) lead	Market Released
--	Any new or previously implanted market-released transvenous right atrial (RA) lead (if applicable)	Market Released
--	Any new or previously implanted market-released transvenous left ventricular (LV) lead (if applicable)	Market Released
Accessory Components		
2090 series	Medtronic CareLink [®] Programmer	Market Released
2490C	Medtronic CareLink [®] Monitor (where applicable)	Market Released
--	Medtronic CareLink [®] Network	Market Released
2067 or 2067L	Medtronic Programming Head (where applicable)	Market Released
DR 220	NorthEast Monitoring Holter Monitor	Market Released

* Will be market released prior to study start in the respective geographies.

3.1 Medtronic TYRX[™] Absorbable Antibacterial Envelope

The Medtronic TYRX[™] Absorbable Antibacterial Envelope is an absorbable sterile prosthesis designed to hold a pacemaker pulse generator or defibrillator to create a stable environment when implanted in the body. The TYRX envelope is constructed from multifilament knitted mesh (polymer made of glycolide, caprolactone, and trimethylene carbonate) that is coated with an absorbable polyarylate polymer. The purpose of the absorbable coating is to act as a carrier for the antimicrobial agents. Animal data demonstrates that the absorbable antibacterial envelope absorbs in approximately 9 weeks. The TYRX envelope is made of an absorbable polymer coating containing the antimicrobial agents rifampin and minocycline in concentrations of 102 µg/cm² for both the medium size (IPG) and large size (ICD) envelopes. The TYRX envelope releases the antimicrobial agents for a minimum of 7 days to reduce the risk of infection of the implanted CIED following surgery. No study site-related activities will occur in a respective geography until the TRYX envelope is commercially available, unless pre-market use for clinical trials is allowed per local regulations and law.

3.2 Market-Released Medtronic IPG, ICD, CRT-P or CRT-D Device

3.2.1 IPG

Subjects who enroll in the study must be scheduled for a generator replacement with a Medtronic IPG or, in the case of a revision, must have an existing Medtronic IPG implanted. The Medtronic IPG must have received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Examples from the Medtronic family of devices include but are not limited to the Adapta, Advisa, Ensura, Relia, Revo, Sensia, or Versa. Other devices may become available during the course of the clinical study and may be used if the aforementioned criteria are met. The device must not have been previously implanted in another patient.

3.2.2 CRT-P

Subjects who enroll in the study must be scheduled for a generator replacement or upgrade with a Medtronic CRT-P or, in the case of a revision, must have an existing Medtronic CRT-P implanted. The Medtronic CRT-P must have received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Examples from the Medtronic family of devices include but are not limited to the Consulta, Syncra, or Viva XT. Other devices may become available during the course of the clinical study and may be used if the aforementioned criteria are met. The device must not have been previously implanted in another patient.

3.2.3 ICD

Subjects who enroll in the study must be scheduled for a generator replacement or upgrade with a Medtronic ICD or, in the case of a revision, must have an existing Medtronic ICD implanted. The Medtronic ICD must have received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Only Medtronic ICDs with SmartShock™ Technology, which includes the RV Lead Noise Discrimination and RV Lead Integrity Alert algorithms, are permitted. The Medtronic family of SmartShock™ Technology ICDs include Evera S, Evera XT, Protecta, and Protecta XT. Other devices may become available during the course of the clinical study and may be used if the aforementioned criteria are met. The device must not have been previously implanted in another patient.

3.2.4 CRT-D

Subjects who enroll in the study must be scheduled for a *de novo* Medtronic CRT-D implant, a generator replacement or upgrade with a Medtronic CRT-D, or, in the case of a revision, must have an existing Medtronic CRT-D implanted. The Medtronic CRT-D must have received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the implant will take place. Only Medtronic CRT-Ds with SmartShock™ Technology, which includes the RV Lead Noise Discrimination and RV Lead Integrity Alert algorithms, are permitted. The Medtronic family of SmartShock™ Technology CRT-Ds include Brava, Brava Quad, Protecta, Protecta XT, Viva S, Viva S Quad, Viva XT, and Viva XT Quad. Other devices may become available during the course of the clinical study and may be used if the aforementioned criteria are met. The device must not have been previously implanted in another patient.

3.2.5 RV Defibrillation Lead Monitoring Features

ICD and CRT-D devices utilized in the WRAP-IT study include four features designed to monitor lead integrity:

1. The RV lead noise discrimination (RV LND) feature analyzes the far-field EGM signal at each near-field sensed event to differentiate sinus rhythm on the far-field EGM (RV lead noise on near-field) from true VT/VF. If sinus rhythm is identified when these signals are compared, VT/VF detection therapy is withheld, and an RV Lead

- Noise alert is triggered both as a tone to warn the subject and as a CareAlert notification to warn the clinician. The RV LND feature is nominally programmed ON.
2. The RV lead integrity alert (RV LIA) feature monitors RV pacing lead impedance for abrupt impedance changes, the frequency of rapid non-sustained VT episodes, and the frequency of very short ventricular intervals counted on the Sensing Integrity Counter. If two of these three criteria are satisfied, an RV LIA alert is triggered as an audible tone to warn the subject and as a CareAlert to warn the clinician. The RV LIA feature is nominally programmed ON.
 3. The RV pacing impedance (P/S impedance) alert both sounds an audible alert and sends a CareAlert if the P/S impedance is lower than the lower programmable threshold (nominally 200 Ω) or higher than the upper programmable threshold (nominally 3000 Ω).
 4. The HV defibrillation impedance (HV impedance) alert both sounds an audible alert and sends a CareAlert if the HV impedance on the RV coil or SVC coil is lower than the lower programmable threshold (nominally 20 Ω) or is greater than the upper programmable threshold (nominally 200 Ω).

An RV lead alert produced by any four of these lead monitoring features may indicate an RV lead system event (LSE). Additionally, other sources of lead noise or impedance change such as the presence of electromagnetic interference (EMI), T-wave oversensing, or R-wave double counting may also trigger one of the lead monitoring features.

3.3 Market-Released Lead(s)

Any market-released, commercially available transvenous lead(s) may be used in this study. Any RV, RA and LV lead may be used, if applicable and compatible with the device. Any lead under recall, even if not in the country of implant, should not be implanted in study subjects; however, active leads previously implanted under recall may be connected to the study device, if previously implanted.

3.4 Market-Released Medtronic CareLink[®] Monitor and Medtronic CareLink[®] Network

The Medtronic CareLink[®] Monitor and the Medtronic CareLink[®] Network are indicated for use in the transfer of patient data from some Medtronic implantable cardiac devices based on physician instructions and as described in the product manual. These products are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician.

The Medtronic CareLink[®] Network enables subjects to remotely transfer data from their device to the clinic. Subjects may be requested to use the Medtronic CareLink[®] Monitor to send their device data to the clinic. Study site personnel can access the data by logging onto the CareLink[®] website via the internet.

The use of the Medtronic CareLink[®] Home Monitor is not required for this study and it may not be available in all participating geographies. However, if the subject uses CareLink[®] to transmit their device data, the data may be used in the analysis of the study objectives, where allowed by local law.

3.5 Market-Released Medtronic CareLink® Programmer

Medtronic's market-released Model 2090 CareLink® programmer (or future models, which become market released in the geographies where this study takes place) must be available at each site to support study visits. Programmers will be used to gather lead electrical data, interrogate devices, program devices, and save device data.

3.6 Additional system components

A subset of subjects in this study may be required to use the market-released model DR 220 Holter Monitor (NorthEast Monitoring, Inc., Maynard MA). The DR220 Holter monitor system communicates with Medtronic implanted devices via telemetry.

4 REGULATORY COMPLIANCE

The WRAP-IT study is a single-blinded, randomized, prospective, multi-center, single blinded post-market, interventional clinical study. This study is required to be in compliance with the Clinical Investigation Plan (CIP), Clinical Trial Agreement (CTA) and local laws/regulations within the respective geographies in which the study is being conducted.

The WRAP-IT clinical study is designed to reflect the Good Clinical Practice (GCP) principles and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical study, and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The study will also be conducted in accordance with the Declaration of Helsinki (2013). The principles of the Declaration of Helsinki have been implemented through the Patient Informed Consent (PIC) process, Ethics Board/IRB/MEC (all henceforth referred to as an "Ethics Committee") approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment, and publication policy.

- In EMEA, local laws and regulations will be followed.
- In the US, the study will be conducted in compliance with 21 CFR Parts 11, 50, and 56.
- In Greater China (Hong Kong), applicable local regulations will be followed.
- In New Zealand, local laws and regulations will be followed.
- In ASEAN (Singapore and Malaysia), local laws and regulations will be followed.
- In India, applicable India laws and regulations will be followed.
- In Latin America, local laws will be complied with.

For additional countries added at a later time, local laws and regulations will be followed. Geography-specific requirements will be documented under a separate cover.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAA) and Declaration of Helsinki on <http://clinicaltrials.gov> (PL 110-85, Section 810 (a)).

Approval of the CIP is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (by signing the CTA or the CIP signature page)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent Ethics Committee.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at that site.

Each site's Ethics Committee will also be required to approve any subject recruitment materials prior to use in the study, if applicable.

5 METHODOLOGY

5.1 Study design

The WRAP-IT study is a randomized, prospective, multi-center, single blinded, post-market, interventional clinical study. The study has three purposes. First, the WRAP-IT study will serve as a post-approval study for those geographies requiring a post-approval study to facilitate collection of complications related to the Cardiovascular Implantable Electronic Device (CIED) implant procedure or system in subjects randomized to receive the TYRX™ Absorbable Antibacterial Envelope (TYRX envelope). Next, this study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, revision, or the implant of a *de novo* CRT-D system. Subjects undergoing CIED generator replacement, upgrade, or revision, or the implant of a *de novo* CRT-D system with a new CIED will be randomized to either receive the TYRX envelope or not to receive the TYRX envelope. Randomization will be 1:1 and be stratified by study site and device type high power (ICD and CRT-D) vs. low power devices (IPG and CRT-P). Finally this large device study provides the unique opportunity to prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead.

5.2 Study objectives

5.2.1 Primary objective

The primary study objective is to compare the rate of major CIED infections through 12-months post-procedure between the TYRX envelope group and the control group (no TYRX envelope).

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. [24,38,43,46,74-76](#) See Appendix A for specific details.

Major CIED infections are defined as CIED infections resulting in one or more of the following:

- CIED system removal
- Any invasive procedure (e.g. pocket opened) without system removal
- Treatment with antibiotic therapy if the subject is not a candidate for system removal and infection recurrence after completion of antibiotic therapy or evidence of deep infection with wound dehiscence, erosion, or purulent drainage.
- Death

Note: All other CIED infections including superficial incisional SSIs that meet the CDC criteria, independent of the time from surgery, are defined as minor CIED infections unless they meet the major CIED infection criteria.

5.2.2 Secondary objectives

- Secondary Objective #1:

Confirm that the TYRX envelope does not increase the CIED procedure-related or system-related complication rate through 12-months post-procedure.

- Secondary Objective #2:

Compare the major CIED infection rate during the entire follow-up between the TYRX envelope group and the control group.

- Secondary Objective #3:

Compare the rate of major and minor CIED infections through 12-months post-procedure between the TYRX envelope group and the control group.

5.2.3 Ancillary objectives

- Compare all-cause mortality rates between the TYRX envelope group and the control group
- Evaluate the CIED procedure success rate in the TYRX envelope group and the control group
 - Control: device and leads all implanted
 - Treatment: TYRX envelope, device, and leads all implanted
- Summarize the adverse events
- Identify the predictors of CIED infection
- Summarize quality of life
- Evaluate the cost effectiveness of the TYRX envelope

[REDACTED]

5.3 Subject selection criteria

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria.

Subjects are considered enrolled in the study upon signing the PIC. Informed consent must be obtained prior to performing any of the study-related procedures. The complete informed consent process will include giving the subject adequate information about the study and ensuring that there is a sufficient amount of time to comprehend the information in the PIC and have all questions answered before making a decision to participate in the study and audio-video record the consent process when applicable per local laws and regulations.

5.3.1 Inclusion criteria

Patients must meet the following inclusion criteria to be eligible to participate in the study:

- Patient is willing to sign and date the study PIC form
 - Patient is at least 18 years of age and meets age requirements per local law
 - Patient is planned to undergo at least one of the following:
 - a. Patient has existing CIED and is undergoing IPG (including CRT-P), ICD or CRT-D replacement or upgrade with a new Medtronic generator
 - i. Subjects planned to have leads added, or extracted and added for upgrades can be enrolled
- OR
- b. Patient will undergo a *de novo* Medtronic CRT-D system implant per approved indications
- OR
- c. Patient has existing study eligible Medtronic CIED in which the pocket was not accessed within the last 365 days, and is undergoing pocket or lead revision
-
- Willing to provide the contact information for the physician who provides follow-up for his/her CIED.
 - Willing and able to comply with scheduled follow-up and study related activities.

5.3.2 Exclusion criteria

Patients must not meet any of the following exclusion criteria to be eligible to participate in the study:

- Known allergy to minocycline or rifampin or their derivatives, or any other known contraindications to implantation of the TYRX envelope.
- Current therapy with chronic oral immunosuppressive agents or $\geq 20\text{mg/day}$ of Prednisone or equivalent.
- Hemodialysis or peritoneal dialysis.
- Prior Cardiac transplantation or existing Ventricular Assist Device (VAD).
- Require long-term vascular access for any reason.

- Prior history of a CIED infection, other prosthetic device infection, or endovascular infection, including endocarditis, in the past 12 months.
- Physical, clinical, or laboratory signs or symptoms consistent with an active infection (including but not limited to pneumonia, urinary tract, cellulitis, or bacteremia)
- Systemic lupus erythematosus, because minocycline has been reported to aggravate this condition
- Female patient who is pregnant, or of childbearing potential and not on a reliable form of birth control. Women of childbearing potential are required to have a negative pregnancy test within 7 days prior to device procedure
- Participation in another study that may confound the results of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager.

5.4 Randomization

Enrolled subjects are eligible for randomization after completion of the baseline assessment if all inclusion and none of the exclusion criteria are met. Subjects will be randomized in a 1:1 fashion to receive the TYRX envelope during their CIED procedure (treatment group) or not to receive the TYRX envelope during their CIED implant/revision procedure (control group).

Subjects will be randomized using an electronic randomization system according to the randomization schedule generated by a Medtronic statistician or designee. The randomization schedule will be stratified by study site and device type (high power or low power devices) to ensure that within each study site and device type randomization is 1:1. Since randomization must occur prior to the CIED procedure, it is recommended that randomization occur as close as possible, but prior to the procedure to minimize study attrition following randomization but prior to the CIED procedure.

Once subjects are assigned to a study group (TYRX envelope or control), they are considered randomized and will be included in the analysis using their randomized assignment regardless of which therapy was actually received. All randomized subjects should be encouraged to comply with the WRAP-IT study procedures until study closure.

5.5 Blinding

Due to the nature of the CIED procedure, it is not possible to blind the implanting investigator or study site staff. However, efforts should be employed to blind the study subject to their randomized treatment throughout the duration of the study. In particular, efforts to keep the subject blinded to their randomized treatment in the procedure room will be necessary in the setting of conscious sedation.

All randomized subjects will be unblinded at the end of the study.

5.6 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be evaluated at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to randomization.
- Subjects will be randomly assigned to their treatment assignment.
- Subjects will be blinded to their randomized treatment assignment.
- Subject demographics, medical history, and CIED procedure information will be collected at baseline and at CIED procedure to allow collection of possible differences that may affect the study's primary endpoint.
- To ensure widespread distribution of data between sites, the maximum number of randomized subjects per site is no more than 100.
- Data collection requirements and study procedures will be standardized across all sites and geographies.
- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials. All study clinicians will be trained on and required to follow the CIP.
- Regular monitoring visits will be conducted for adherence to the CIP and to verify source data.
- An independent clinical events committee (CEC) will regularly review and adjudicate all reported adverse events. The CEC will not be informed of the treatment group when adjudicating adverse events. However, the CEC may be able to infer the treatment group in cases where an adverse event is potentially related to the TYRX envelope.
- A statistical analysis plan will be developed prior to analyzing the study's primary or secondary objectives.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

6 STUDY PROCEDURES

Prior to performing study related procedures, all sites must have Ethics Committee and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

Medtronic representatives may provide support as required for the study under supervision of the Principal Investigator, including:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites

6.1 Investigator / Investigation site selection

All clinical investigators managing the subject's cardiac rhythm disease must be qualified practitioners and experienced in the diagnosis and treatment of subjects with cardiac rhythm disease. All implanting physicians must be experienced and/or trained in the handling of CIEDs.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical study.
- Be experienced in the field of application and training in the use of CIEDs.

The principal investigator shall be able to demonstrate that the proposed investigational site:

- Has the required number of eligible subjects needed within the recruitment period.
- Has one or more qualified investigators, a qualified study team and adequate facilities for the foreseen duration of the clinical study.
- Has required infrastructure and personnel to ensure audio-visual recording of the informed consent procedure, where required as per local requirements.

Site personnel training and delegation will be completed prior to participation in this clinical study.

6.2 Site initiation

During the initiation process (prior to subject enrollment), Medtronic will train site personnel on the Clinical Investigation Plan, relevant standards and regulations, if needed, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

A CTA shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigation site as per the local legal requirements, and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement the investigator indicates approval of the CIP

Prior to performing study related activities, all sites must have Ethics Committee approval, as applicable for that geography.

All local and regional regulatory requirements will be fulfilled prior to site initiation and enrollment of subjects into the study. Each study site must have written documentation of site and investigator readiness before beginning any study-related activities.

Requirements for initiation vary by geography, and may include, but are not limited to:

- Written documentation of Ethics Committee approval of the current version of the CIP and PIC (approved versions must be retrievable from the Ethics Committee approval letter or submission letter) and voting list, as required by local law,
- Regulatory authority approval or notification (as required per local law)
- Executed CTA on file with sponsor
- Current Curriculum Vitae (CV) of investigators
- Documentation of delegated tasks
- Documentation of study site personnel training

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed, if appropriate. Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to subject enrollment.

6.3 Equipment requirements

The following equipment must be available at each site to support study activities:

- Access to a clinical lab to test and obtain the results of bacterial cultures collected from any suspected infection.
- Access to equipment to collect a chest X-ray image of the CIED system in the instance of a suspected LSE.
- Site has the access to high speed internet to submit data through an internet based interface.

Calibration and maintenance of equipment listed above will be done by the site according to hospital practice (documented proof of said activities should be available upon request by Medtronic).

6.4 Data collection

Data collection requirements are summarized in

Table 5.

Clinical data will be collected at baseline, procedure/pre-hospital discharge, and every 6-months following CIED procedure until study closure. Data will be collected using electronic case report forms (eCRFs) using an electronic data management system for clinical studies. In addition to eCRF data, non-eCRF data will be collected which includes: device interrogation files, CareLink[®] transmission files, and Holter files. Data will be stored in a secure, password-protected database, which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports will be generated by Medtronic to monitor data quality and study progress. At the end of the study, the data will be frozen and retained indefinitely by Medtronic.

Table 5: Data collection and study procedure requirements at subject visits

Study Procedure	Baseline	Procedure	Pre-Hospital Discharge	Biannual Follow-up Visits	Unscheduled Visit	Study Exit
Patient Informed Consent	X					
Inclusion/Exclusion Assessment	X					
Subject Demographics	X					
Record Medications ¹	X	X	X	X	X	X
Medical History	X					
System and Procedure Information		X				
Confirm Programming Requirements (subjects with ICD or CRT-D only)		X	X	X		
Evaluate Subject for Signs and Symptoms of CIED Infection			X	X	X	X
Evaluate Subject and Device for LSEs			X	X	X	X
Final Device Interrogation / CareLink [®] Transmission		X	X	X	X	X

Study Procedure	Baseline	Procedure	Pre-Hospital Discharge	Biannual Follow-up Visits	Unscheduled Visit	Study Exit
EQ-5D	X			X (12 month visit only)		X (Only if exited prior to 12 month visit)
Collect or Confirm Contact Information of CIED follow-up Physician ²	X		X	X		
Exit Subject						X
CIED Infection	As they occur					
CIED Infection-Related Health Care Utilization	As they occur					
CIED Infection-Related EQ-5D	Within 2 weeks following a diagnosis of CIED infection, and subsequently 1, 3, and 6 months post infection diagnosis					
Lead System Event (ICD and CRT-D Subjects only)	As they occur					
Holter for Suspected LSE if required (ICD and CRT-D Subjects only)	As they occur					
Adverse Events (AEs)	As they occur					
Device Deficiencies	As they occur					
System Modifications	As they occur					
Study Deviations	As they occur					
Device Disposition for TYRX envelope	As it occurs in geographies where required					
Death	As it occurs					

¹ Record any anti-platelet agents, anticoagulants, antibiotics, corticosteroids, insulin or oral diabetic agents.

² The CIED follow-up physician could also be the referring cardiologist or other physician overseeing care of the patient following procedure.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key-coded form unless it is impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier (such as x-rays). Participating subjects will not be identified by name in any published reports about the study.

6.5 Patient informed consent process

Patient informed consent (PIC) is defined as a legally effective documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision

to participate. This process includes obtaining a PIC and a/an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's Ethics Committee and signed and dated by the subject (or their legally authorized representative or guardian). A subject may only consent after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. Informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical study and in accordance with local law. In such cases, the subject shall also be informed about the clinical study within his/her ability to understand.

Prior to enrolling subjects, each site's Ethics Committee will be required to approve the PIC and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. Any changes to a previously approved PIC throughout the course of the study must be reviewed and approved by Medtronic and the Ethics Committee reviewing the application before being used to consent a prospective study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by Medtronic and the Ethics Committee. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing informed consent in writing.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject (or their legally authorized representative or guardian). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The process of obtaining patient informed consent shall:

- Ensure that the principal investigator or an authorized designee conducts the PIC process.
- Include all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the PIC and Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language as required by law are given to the subject (or their legally authorized representative or guardian) in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the PIC to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject (or legally authorized representative or guardian if applicable) acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the PIC process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- In addition to the requirement of obtaining written informed consent, audio-visual recording of the informed consent process of each trial subjects, including the

procedure of providing information to the subject and his/her understanding on such consent is required to be done while adhering to the principles of confidentiality, where required by local regulations or Ethics Committee requirements. Such audio-visual recording and related documentation would be preserved.

- Provide the subject with a copy of the PIC, the Authorization to Use and Disclose Personal Health Information/Research Authorization/HIPAA/other privacy language and any other written information, signed and dated if required by local law.
- Ensure the subject (or their legally authorized representative or guardian) are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If the patient informed consent is obtained the same day the subject begins participating in study-related procedures, it must be documented that consent was obtained prior to participation in any study-related procedures. It is best practice for the PIC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the PIC. The patient informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The PIC and any other information must be read aloud and explained to the prospective subject or his/her legally authorized representative. The witness signs and personally dates the PIC attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the PIC as well. The PIC should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed and dated PIC must be filed in the hospital/clinical chart or with the subject's study documents.

The PIC and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing. Any designated Medtronic personnel who support the procedure must be able to review the subject's signed and dated PIC and verify its completeness prior to proceeding with the procedure. In the event the designated Medtronic personnel identify PIC as being incomplete, the procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

Refer to Appendix F: Patient Informed Consent Templates for the sample PIC(s).

6.6 Enrollment/Baseline

When a patient (or legally authorized representative or guardian if applicable) and the principal investigator or authorized designee (if applicable) signs and dates the PIC, the patient is considered a subject enrolled in the study. The date the subject signed the PIC and data protection authorization must be documented in the subject's medical

records. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Medtronic should be notified (via Enrollment Notification eCRF) as soon as possible to aid in enrollment tracking. Once consent is obtained, report adverse events, device deficiencies, study deviations, system modifications, and subject exits or deaths as they occur.

The baseline visit can be a stand-alone visit or can be performed on the same day as, but prior to the procedure. Women of childbearing potential should practice birth control 30 days prior to CIED generator replacement, upgrade, revision, or *de novo* CRT-D implant and are required to have a negative pregnancy test within 7 days prior to device procedure.

The following information is required to be collected at the baseline visit:

- Patient Informed Consent Date (Enrollment Date)
- Eligibility Verification (Inclusion/Exclusion Assessment)
- Patient Demographics
- Medications
- Relevant Medical History
- Collect contact information of the CIED follow-up physician and/or referring cardiologist or any other referring physician in the patient chart.
- EQ-5D

6.6.1 Eligibility Verification (Inclusion/Exclusion)

Confirm subjects meet all inclusion criteria and none of the exclusion criteria. It is not a study deviation if eligibility violations are discovered after signing the informed consent but prior to randomization or attempting a CIED procedure. However, subjects with eligibility violations discovered prior to randomization should be exited **prior** to randomization. Eligibility violations discovered after randomization require a study deviation, but these subjects should continue to be followed per intention-to-treat principles.

6.6.2 Relevant Medical History

The subject's relevant medical history including cardiovascular medical history, indicators of severity of disease state (e.g. NYHA classification), and CIED device history (e.g. number of previous systems, leads) will be collected.

6.6.3 Medications

Record the use of any anti-platelet, anticoagulant, antibiotics, corticosteroids, insulin, or oral diabetic agents at baseline.

6.7 CIED Procedure

Prior to procedure, but as close as reasonably possible to the CIED procedure, randomly assign the subject to either the TYRXTM Absorbable Antibacterial Envelope group or control group using the electronic randomization system. The randomization schedule automatically gets populated on the eCRF. All randomized subjects must be implanted

with a Medtronic CIED shown in Table 4, as the ancillary objectives will require data collection from the device via a device interrogation. If a non-Medtronic CIED is implanted, the subject should remain in the study per intention-to-treat principles, but a study deviation is required. Non-Medtronic leads are allowed.

6.7.1 Infection Control Strategies

Standard strategies to minimize the risk of infection utilized during the CIED procedure include recommendations to:

- Ensure that the subject does not have any clinical signs of infection prior to the CIED implant including absence of fever for 48 hours prior to the procedure.
- Administer prophylactic parenteral antibiotics immediately prior to the CIED implant per guidelines.²³
- Pre-operative antiseptic preparation of the surgical site.
- Avoid shaving the operative site: clip if necessary.
- Maintain proper sterile technique throughout the replacement or upgrade procedure.
- Compulsive attention to the maintenance of sterile technique throughout the replacement or upgrade procedure.
- Utilize separate tables for instruments and gowns/gloves.
- Mechanically wash the pocket. *Note:* avoid using iodine and providone as indicated in the TYRX Envelope Instructions for Use.
- Prevent or minimize hematoma formation by meticulous cautery of bleeding sites.
- Management of perioperative anticoagulation should be individualized. If Warfarin is continued, INR at time of procedure should be less than 3.0 and less than 3.5 for patients with mechanical valves.⁸¹
- Resume any necessary systemic anticoagulation post procedure with caution to avoid pocket hematoma formation. Low molecular heparin immediately post procedure should be avoided.
- At the time of this protocol version there are no data to support the administration of postoperative antibiotic therapy, and it is not recommended because of the risk of drug adverse events, selection of drug resistant organisms, and cost.²³

6.7.2 CIED replacement, upgrade, revision, or implant

- Perform any site specific standard of care pre-operative laboratory assessments if not already completed during the screening period.
- Perform the CIED replacement, upgrade, revision or implant of *de novo* CRT-D system following site standard of care procedures ensuring that the infection control strategies outlined above are considered.
- For subjects randomized to the TYRX envelope group, implant the TYRX envelope following its instructions for use. *Note:* removal of part of the TYRX envelope for resizing may decrease the amount of antibiotic on the TYRX envelope.
- Do not use the TYRX envelope for those subjects randomized to the control group.
- Complete procedure eCRF

A CIED procedure attempt occurs when the device pocket is opened or venous access was gained (i.e. skin was cut). All procedure attempts should be recorded on a procedure eCRF. If the device remains in the body following the procedure attempt, any future revisions to the system once the CIED remains in the body following pocket closure require a system modification eCRF to be completed. (For example, an additional LV lead implant attempt several days after an implant attempt where the CIED remains in the body, but the LV lead could not be placed require an implant eCRF for the CIED implant and a system modification eCRF for the additional LV lead implant attempt).

Subjects undergoing a procedure attempt where the CIED does not remain in the body following the procedure completion may undergo another CIED procedure attempt on the same or separate date per the site's standard medical practice. Each CIED procedure attempt should be recorded on a new procedure eCRF. However, subjects with a procedure attempt who never have a CIED chronically placed in the body should continue with study follow-up per intention-to-treat principles.

6.7.3 Required Programming (ICD and CRT-D devices only)

[Redacted]

[Redacted]

[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]

EGM vectors for VR	EGM1: RVtip-RVring EGM2: Can-RVcoil EGM3: RVtip-RVcoil LECG: Can-SVC (<i>Note: SVC electrode must be present for this configuration</i>)	EGM1: RVtip-RVring EGM2: Can-RVcoil EGM3: RVtip-RVcoil LECG: Can-SVC (<i>Note: SVC electrode must be present for this configuration</i>)
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6.7.4 Final System Configuration

Record the final system configuration. This will include the serial number and location of the implanted CIED device and active leads.

6.7.5 Final Device Interrogation

At the end of the procedure, perform a device interrogation and save on a USB flash drive or other removable electronic media. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility. A deviation is required if a device interrogation is missed.

6.7.6 Assessment for AE/SAEs

Document any reportable AE/SAEs including AEs related to CIED infections or lead system events (refer to section 9 Adverse Events and Device Deficiencies).

6.8 Pre-hospitalization Discharge

The following actions are required prior to hospital discharge:

- Evaluate subject for signs and symptoms of CIED infection. If CIED infection suspected see section 6.11.
- Educate subject on signs and symptoms of CIED infection and remind subject to contact their device follow-up clinic if they have signs or symptoms of CIED infection
- Record the use of any anti-platelet, anticoagulant, antibiotics, corticosteroids, insulin, or oral diabetic agents
- Perform a device interrogation and save on a USB flash drive or other removable electronic media. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility. A deviation is required if a device interrogation is missed.
- Verify contact information of CIED follow-up physician
- Document any reportable AEs

Subjects with ICD or CRT-D only:

○



○



6.9 Scheduled follow-up visits

After receiving notice of a successful procedure (or unsuccessful procedure if a future CIED procedure attempt is not planned), Medtronic will provide the target dates and windows for each visit to the implanting site. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation. Follow-up visit windows are listed in Table 7 and are based on days post-CIED procedure.

Table 7: Data collection and study procedure requirements at subject visits

Study Follow-up Visit	Window (Calculated days post-CIED procedure)		
	Window Start (days post-procedure) ¹	Target (days post-procedure)	Window End (days post-procedure)
6-Month	168	183	198
12-Month	365	365 ²	395
18-Month	521	549	577
24-Month	702	730	758
30-Month	887	915	943
36-Month	1070	1098	1126

¹Days post-randomization if subject never had a CIED procedure attempt.

²The target date and window start date intended to be equal for primary objective analysis purposes.

It is recommended that scheduled follow-up visits occur in the clinic where device interrogations can occur; however, remote visits via telephone are an acceptable alternative in cases where the patient utilizes the CareLink[®] Network and when a clinic visit is not possible. If the follow-up visit is conducted via telephone and CareLink[®], review the subject's CareLink[®] transmission and review the subject's medical records (hospitalizations, emergency department visits) and assess for adverse events, including any system related events and CIED infections prior to making phone call.

The following information is required to be collected at the follow-up visit:

- Assess subject for CIED infection
 - If CIED infection is suspected refer to section 6.11
- Document any reportable AEs (refer to section 9 Adverse Events and Device Deficiencies)
- Record current use of any anti-platelet, anticoagulant, antibiotics, corticosteroids, insulin, or oral diabetic agents at the time of the visit

- Verify contact information of CIED follow-up physician
- For follow-up visits occurring in the clinic, perform a device interrogation and save on a USB flash drive or other removable electronic media. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility. A deviation is required if a device interrogation is missed.
- If the follow-up visit occurs via telephone, ensure the subject has completed a CareLink transmission prior to the telephone follow-up. Deviations are required for telephone follow-up visits not associated with a CareLink transmission.
- Schedule the next follow-up visit
- EQ-5D (12-month visit only)

Subjects with a ICD or CRT-D only:

- Assess subject and review device diagnostics for LSEs (lead failures, lead dislodgements, lead perforation, or header connector issues). If a LSE is suspected refer to section 6.12.
- Review all device alerts. If LIA, LNA, or impedance out of range alerts are present update the device alert log eCRF. Report any reprogramming or system modifications associated with the device alert.
- Confirm required programming in Table 6

6.10 Unscheduled follow-up visits

An unscheduled visit is defined as any non-standard of care visit to the study site for reasons related to the implanted CIED system including suspected CIED infection and any device alerts. The following procedures are required at each unscheduled visit:

- Assess subject for potential CIED infection. If a CIED infection is suspected see section 6.11.
- Record current use of any anti-platelet, anticoagulant, antibiotics, corticosteroids, insulin, or oral diabetic agents at the time of the visit
- Document any reportable AEs (refer to section 9 Adverse Events and Device Deficiencies)
- Perform a device interrogation and save on a USB flash drive or other removable electronic media. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility. A deviation is required if a device interrogation is missed.

Subjects with an ICD or CRT-D only:

- Assess subject and review device diagnostics for LSEs (lead failures, lead dislodgements, lead perforation, or header connector issues). If a LSE is suspected see section 6.12.

- Review all device alerts. If LIA, LNA, or impedance out of range alerts are present, update the device alert log eCRF. Report any reprogramming or system modifications associated with the device alert.

6.11 Potential CIED Infection

Infection related information should be reported for each suspected CIED infection. The actions should be taken:

- Collect source documents including any physician notes, admission/discharge summaries, microbiology reports, echocardiograms, invasive procedure reports, and antibiotic administration records)
- Complete infection eCRF
- Verify that an AE for the potential CIED infection was reported on an AE eCRF
- Complete a system modification eCRF if CIED system revised
- Obtain healthcare utilization information for all hospitalizations, emergency department visits, urgent visits, and clinic visits associated with the CIED infection diagnosis.
- Complete UB-04 collection where UB-04 forms and data are available
- Perform a device interrogation and save on a USB flash drive or other removable electronic media. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility. A deviation is required if a device interrogation is missed.
- Administer the EQ-5D quality of life assessment within two weeks of the infection diagnosis and again at approximately 1-month, 3-months, and 6-months post-infection diagnosis. See Table 8 for CIED related infection assessment windows. EQ-5D questionnaires may be administered remotely via telephone. If any of the infection related EQ-5D assessments coincide with the 12 month follow-up, only one EQ-5D assessment (either infection or 12 month) is required.
- If possible, it is strongly recommended that a photo of the infection site/pocket be obtained.

Table 8: CIED Infection-Related EQ-5D Assessment Windows

CIED Infection EQ-5D Assessment	Window (Calculated days post-CIED infection diagnosis)		
	Window Start (days post-diagnosis) ¹	Target (days post-diagnosis)	Window End (days post-diagnosis)
At Diagnosis	0	NA	14
1-month	23	30	37
3-month	75	90	105
6-month	168	183	198

6.12

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

6.13

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

[REDACTED]

6.14 Device Interrogation

For scheduled follow up and unscheduled follow up visits occurring at the study site, a final device interrogation file (.pdd) must be obtained and saved in a digital format (e.g., floppy, USB). Alternatively, if the follow-up visit occurs remotely over the phone, a CareLink® transmission must be submitted. Store the original file at the site and send a copy to Medtronic. It is recommended that data are not cleared during any interrogation.

6.15 Healthcare Utilization

Health Care Utilization information related to CIED infections will be collected for each suspected CIED infection. All hospitalizations, emergency department visits, urgent care, or unscheduled follow-up visits associated with the suspected CIED infection, regardless of location of care, are considered reportable HCUs for this study.

HCU information will be included in the review of suspected CIED infection by the CEC. Supporting source documentation such as hospital admission/discharge reports or procedure notes may be requested if needed for study or endpoint evaluation.

Additionally, UB04 codes where available will be collected with all healthcare utilizations related to CIED infections.

6.16 System Modification

A system modification will be reported in the event the device and/or leads require invasive modification (e.g., generator or lead explant, generator or lead replacement, lead repositioning, CIED system explant due to infection). This includes instances where additional lead implant attempts are made following a procedure where the CIED remains in the device pocket following the initial CIED procedure. In the event of a system modification, the follow-up schedule for the subject will remain unchanged and will continue to be followed until the end of the study. For a system modification the following activities are required:

- Perform an initial device interrogation prior to the system modification and save on a USB flash drive or other removable electronic media.
- Complete a system modification eCRF
- If the system modification is related to a CIED infection, ensure that an AE, HCU and infection eCRF are completed
- Perform a final device interrogation following the system modification if the subject's device remains in the body or was replaced with a new system and save on a USB flash drive or other removable electronic media.
- Submit copies of the initial and final (if done) device interrogations to Medtronic, with copies being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility.

If the device is taken out of service (e.g., explanted or capped) and a replacement will not be implanted or the replacement is not a study approved device, *the subject will still be followed at the normally scheduled follow-up visits through the end of the study.*

All explanted product (device, leads, etc.) should be returned to the respective manufacturer for analysis when permissible by local laws and regulations.

In the event that a subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via eCRF as separate system modifications.

6.16.1 System Modifications in Subjects Randomized to the TYRX Envelope Group

Subjects randomized to the TYRX envelope group must receive a new TYRX envelope as part of all system modifications where the device pocket is opened and the CIED is removed or replaced.

6.16.2 System Modifications in Subjects Randomized to the Control Group

Subjects randomized to the control group must not receive a TYRX envelope as part of a system modification.

6.17 Subject Exit or Withdrawal

A study exit eCRF is required for all subjects except in the case of death. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs (including CIED infections) are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. Exited subjects will not be replaced with newly enrolled subjects.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study closure
- Subject lost to follow-up (refer to section 6.17.1 for more information)
- Subject did not meet inclusion/exclusion criteria
- Subject was not randomized
- Subject did not provide consent or data use protection authorization
- Subject chooses to withdraw (refer to section 6.17.2 for more information)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met)

For study exit visits for reasons other than subject lost to follow-up the following information is required:

- Assess subject for CIED infection.
- Assess subject for potential CIED infection. If a CIED infection is suspected see section 6.11.
- Document any reportable AEs (refer to section 9 Adverse Events and Device Deficiencies).
- Record current use of any anti-platelet, anticoagulant, antibiotics, corticosteroids, insulin, or oral diabetic agents at the time of the visit.
- For study exit visits occurring in the clinic, perform a device interrogation and save on a USB flash drive or other removable electronic media. Device interrogation data must be sent to Medtronic, with a copy being maintained at the site in the subject's file. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility. A deviation is required if a device interrogation is missed.
- If the study exit visit occurs via telephone, ensure the subject has completed a CareLink transmission prior to the telephone follow-up. Deviations are required for telephone study exit visits not associated with a CareLink transmission.
- Administer the EQ-5D if the subject exit occurs prior to completing the 12 month follow-up visit.
- Document the reason for subject exit or withdrawal.

Subjects with a ICD or CRT-D only:

- Assess subject and review device diagnostics for LSEs (lead failures, lead dislodgements, lead perforation, or header connector issues). If a LSE is suspected refer to section 6.12.
- Review all device alerts. If LIA, LNA, or impedance out of range alerts are present update the device alert log eCRF. Report any reprogramming or system modifications associated with the device alert.

6.17.1 Lost To Follow-Up

In the case that the subject is determined to be lost to follow-up, a minimum of two attempts to contact the subject must be recorded on the eCRF. The recommended method of contact is one letter and one phone record or two letters. In addition, follow the regulations set forth by the governing Ethics Committee.

6.17.2 Subject Withdrawal

A subject will be exited from the study in the event that he or she is unable to participate, expresses a desire to withdraw, or is unwilling to continue participation in the study. In addition, a subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition, if the inclusion/exclusion criteria are not met or other reason. In such cases, the subject will be notified and provided an explanation regarding the reasons for the study exit.

The subject should be informed that their future care or treatment will not be affected in any way as a result of choosing to not participate in this study. Furthermore, alternative treatments and medical consequences of exiting the study should be discussed with the subject. Any significant new findings related to the study that may develop, which may relate to the subject's willingness to continue participation, should be communicated to the subject.

7 INVESTIGATIONAL DEVICE/SOFTWARE STORAGE, HANDLING AND TRACEABILITY

All products used in this study will be market released in the geographies they are used, Device Traceability may be required per local laws and regulations. TYRX™ Absorbable Antibacterial Envelope (if applicable), device and lead information of implanted system will be collected at implant (e.g., model number).

If there are additional local requirements related to implanted information beyond what is collected by Medtronic on the electronic Case Report Form, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the clinical study, lot or batch number).

Commercially available product supply will be managed in a manner consistent with other market-released products.

8 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the eCRF to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Ethics Committee as well as Medtronic within five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with Ethics Committee policies, local laws and/or regulatory agency requirements must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. . Refer to Table 17 for deviation reporting requirements for all geographies and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, and terminate the clinical study). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

For the WRAP-IT study AEs will be collected for all adverse events that are potentially CIED system related (including TYRX envelope related), procedure related, CIED infection related, and all serious adverse events regardless of their relationship to the CIED system or procedure.

9.1 Adverse Event and Device Deficiency definitions

Where the definition indicates “device,” it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. For the purposes of this study, all adverse events will be classified according to ISO 14155:2011.

Table 9: Adverse Event definitions

General	
Adverse Event (AE) (Adapted from ISO 14155:2011, 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the medical device <i>Note 1:</i> This definition includes events related to the device under investigation or the comparator. <i>Note 2:</i> This definition includes events related to the procedures involved.
Adverse Device Effect (ADE) (ISO 14155:2011, 3.1)	Adverse event related to the use of a medical device <i>Note 1:</i> This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device. <i>Note 2:</i> This definition includes any event resulting from an error use or from intentional misuse of the medical device
Device Deficiency (DD) (ISO 141155:2011, 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. <i>Note:</i> Device deficiencies include malfunctions, use errors and inadequate labeling
Relatedness	

<p>CIED system related</p> <p>(includes all implantable components and features, associated introduction tools, operational and download software and programmers necessary for conducting study-related procedures as defined in the Clinical Investigation Plan)</p>	<p><u>Device-related</u>: An adverse event that results from the presence or performance (intended or otherwise) of the device</p> <p><u>RA lead-related</u>: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead</p> <p><u>RV lead-related</u>: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead</p> <p><u>LV lead-related</u>: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead</p> <p><u>Implant tool-related</u>: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool</p> <p><u>Programmer-related</u>: An adverse event that results from the presence or performance (intended or otherwise) of the programmer</p> <p><u>TYRX™ Absorbable Antibacterial Envelope-related</u>: An adverse event that results from the presence or performance of the TYRX™ Absorbable Antibacterial Envelope</p>
<p>CIED procedure related</p>	<p>An adverse event that occurs due to any procedure related to the implantation or surgical modification of the system including the TYRX envelope (if applicable)</p>
<p>CIED infection related</p>	<p>A adverse event resulting from the procedure or surgical modification that results in a CIED infection, which includes:</p> <ul style="list-style-type: none"> • CIED pocket infections • Persistent bacteremia • CIED endocarditis
<p>Seriousness</p>	
<p>Serious Adverse Event (SAE) (ISO 14155:2011, 3.37)</p>	<p>Adverse event that:</p> <ol style="list-style-type: none"> a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in <ol style="list-style-type: none"> 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect <p><i>Note</i>: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.</p>
<p>Serious Adverse Device Effect (SADE) (ISO 14155:2011, 3.36)</p>	<p>Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.</p>
<p>Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2011, 3.42)</p>	<p>Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report</p> <p><i>Note</i>: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.</p>

Complication	<p>An adverse event that includes the following is considered a complication:</p> <ul style="list-style-type: none"> • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention <p>Non-invasive (21 CFR 812): when applied to a diagnostic device or procedure, means one that does not by design or intention:</p> <ul style="list-style-type: none"> • Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or <ul style="list-style-type: none"> ○ Penetrate: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to ○ Pierce: to force a way into or through something • Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os <p><i>Note (FDA):</i> Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.</p>
Observation	<p>Any Adverse Event that is not a complication.</p> <p><i>Note 1:</i> Only system or procedure related AEs will be classified as complication or observation</p>
Major CIED infection	<p>A CIED infection resulting in one or more of the following:</p> <ul style="list-style-type: none"> • CIED system removal • Any invasive procedure (e.g. pocket opened) without system removal • Treatment with antibiotic therapy if the subject is not a candidate for system removal and infection recurrence after completion of antibiotic therapy or evidence of deep infection with wound dehiscence, erosion, or purulent drainage. • Death
Minor CIED infection	<p>All other CIED infections including superficial incisional SSIs that meet the CDC criteria, independent of the time from surgery, are defined as minor CIED infections unless they meet the major CIED infection criteria</p>
Other	

Unavoidable Adverse Event	An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:	
	Event Description	Timeframe (hours) from the Surgical Procedure
	Anesthesia related nausea / vomiting	24
	Low-grade fever (<100°F or 37.8°C)	48
	Pocket site / Incisional pain	72
	Mild to moderate bruising / ecchymosis	168
	Sleep problems (insomnia)	72
	Back pain related to laying on table	72
	Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure	72

9.2 Adverse Event and Device Deficiency Assessment

9.2.1 Adverse Events

Adverse event definitions are provided in Table 9. To ensure that all AEs that are potentially relevant to the WRAP-IT study are collected, all adverse events that are potentially CIED system related (including TYRX envelope related), procedure related, CIED infection related, and all serious adverse events regardless of their relationship to the CIED system or procedure will be collected and reported to Medtronic during the study, starting from the time the subject signs the PIC. Reporting of these events to Medtronic will occur on the AE eCRF.

Each AE must be recorded on a separate AE eCRF and include a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, the relatedness and seriousness of the event, diagnostic tests and procedures performed, actions taken as a result of the event, and the outcome of the event. Serious AEs that are not related to the CIED system or procedure may collect only the necessary information required for regulatory reporting. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. In all geographies, Unavoidable Adverse Events, listed in Table 9 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-CIED procedure.

For AEs that require immediate reporting (see Table 11), initial reporting may be done by phone, fax (refer to Table 1 for sponsor contact information), or on the eCRF completing as much information as possible. The AE eCRF must be completed as soon as possible.

9.2.2 Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not

been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 11).

9.2.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), updated information must be reported by updating the AE eCRF. All adverse events must be followed until the adverse event has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure or system related adverse events, as classified by the investigator, are resolved or they are unresolved with no further actions planned.

At the time of study exit, all adverse events with an outcome of “Unresolved, further actions or treatment planned” must be reviewed and the original AE updated. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study exit.”

9.3 Adverse Events, Device Deficiency Classification and Reporting

All reportable adverse events and device deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event/device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

Regulatory reporting of all safety events, which may include SAEs and device deficiencies that could have led to an SADE, will be completed according to local regulatory requirements. Refer to Table 11 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the Ethics Committee responsible for oversight of the study.

Appendix G contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an adverse event is unexpected in nature. For emergency contact regarding a USADE, SAE and/or SADE, contact a clinical study representative immediately (refer to the study contact list provided in the site’s study documents binder/investigator site file or refer to the contact information provided on the title page).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 10: Adverse Event classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	CIED system-related (Device related, RA lead, RV lead, LV lead, Implant tool, Programmer, TYRX™ Absorbable Antibacterial Envelope related), CIED procedure related, CIED infection related
	Sponsor	CIED system related (Device related, RA lead, RV lead, LV lead, Implant tool, Programmer, TYRX™ Absorbable Antibacterial Envelope related), CIED procedure related, CIED infection related
Severity	Investigator	SAE,
	Sponsor	SAE, USADE, Complication or Observation (for all system, TYRX™ Absorbable Antibacterial Envelope, or procedure related adverse events),
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review and adjudicate at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication/observation classification. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

Table 11: Reporting requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	<p>EMEA: Immediately after the investigator first learns of the event or of new information in relation with an already reported event. <i>(ISO 14155 and local law)</i> All other geographies: Submit in a timely manner after the investigator first learns of the event.</p> <p>India: All serious adverse events shall be reported to the sponsor. <i>(Indian GCP section 3.3.4.3)</i>. It is recommended to report all serious adverse events to the sponsor within 24h. For reported deaths the investigator shall supply any additional information e.g. autopsy report and terminal medical reports. <i>(Indian GCP section 3.3.4.5)</i></p> <p>All other geographies: Report to the sponsor, without unjustified delay, all serious adverse events.</p>
Ethics Committee,	All geographies: Submit to Ethics Committee per local reporting requirement.
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.

Serious Adverse Device Effects (SADEs), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medtronic	<p>EMEA: Immediately after the investigator first learns of the event or of new information in relation with an already reported event. <i>(ISO 14155 and local law)</i></p> <p>India: All serious adverse device effects shall be reported to the sponsor. <i>(Indian GCP section 3.3.4.3)</i>. It is recommended to report all serious adverse events to the sponsor within 24h.</p> <p>All other geographies: Submit in a timely manner after the investigator first learns of the event.</p>
Regulatory Authority	All geographies: As per local reporting requirement.
Ethics Committee	All geographies: Submit per local Ethics Committee requirement.
Sponsor submit to:	
Regulatory authorities	<p>Singapore: All events should be reported immediately and not later than 10 calendar days for events that have led to the death, or a serious deterioration in the state of health, of a patient, a user of the medical device or any other person. <i>(GN-05-R2 section 4)</i></p> <p>New Zealand: Sponsor is required to report all fatal or life-threatening suspected unexpected serious adverse reactions occurring in New Zealand trial participants where the treatment is known. Reports must be sent to Medsafe within 7 days of the sponsor receiving an investigator's report of a USADE. Adverse reactions occurring in a clinical trial participants are considered to be unexpected if they are not outlined in the protocol and investigator's brochure, and are not defined study end-points (e.g. death or hospitalization). <i>(Guideline on the Regulation of Therapeutic Products in New Zealand – Part 11- Edition 1.2 section 5.4.2)</i></p> <p>All other geographies: Submit to regulatory authority per local reporting requirement.</p>
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.
Adverse Device Effects	
Investigator submit to:	
Medtronic	<p>EMEA: Immediately after the investigator first learns of the effect. <i>(ISO 14155 and local law)</i></p> <p>All other geographies: Submit in a timely manner after the investigator first learns of the effect.</p>
Regulatory authority	All geographies: As per local reporting requirement.
Ethics Committee	All geographies: Reporting timeframe as per local Ethics Committee requirement.
Sponsor submit to:	
Regulatory authorities	<p>Singapore: All adverse device effects that represents a serious threat to public Health should be reported immediately and not later than 48 hours. <i>(GN-05-R2:Guidance on the Reporting of Adverse Events for Medical Devices section 4)</i></p> <p>All events that occur outside of Singapore but where the medical devices have also been supplied in Singapore do not require reporting unless:</p> <ul style="list-style-type: none"> • the registration or license conditions of those medical devices require so, or • a notice requesting for adverse event information has been issued by the Authority. <i>(GN-05-R2 section 2)</i> <p>All other geographies: Submit to regulatory authority per local reporting requirement.</p>
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.

All other reportable Adverse Events	
Investigator submit to:	
Medtronic	All geographies: Submit in a timely manner after the investigator first learns of the event.
Regulatory Authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	New Zealand: Sponsor is required to hold reports of all (worldwide) USADEs. These reports should not be routinely sent to Medsafe, but must be held in an accessible form and made available to Medsafe on request. (<i>Guideline on the Regulation of Therapeutic Products in New Zealand – Part 11- Edition 1.2 section 5.4.3</i>) All other geographies: Submit to regulatory authority per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	EMEA: Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. All other geographies: Submit or report as required per local reporting requirements.
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	Singapore: All events should be reported immediately and not later than 30 calendar days for events where a recurrence of which might lead to the death, or a serious deterioration in the state of health, of a patient, a user of the medical device or any other person. (<i>GN-05-R2 section 4</i>) All geographies: Submit to regulatory authority per local reporting requirement.
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	All geographies: Submit in a timely manner after the investigator first learns of the event.
Regulatory Authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Ethics Committee	All geographies: Submit to Ethics Committee per local reporting requirement.
New information that may adversely affect safety of the subjects or the conduct of the study	
Investigator submit to:	
Medtronic	India: Investigator shall promptly report to sponsor and monitor new information that may adversely affect safety of the subject or the conduct of the study. (<i>Indian GCP section 3.3.4.4</i>). All other geographies: Submit in a timely manner after the investigator first learns of the event.
Ethics Committee	India: Investigator shall promptly report new information that may adversely affect safety of the subject or the conduct of the study. (<i>Indian GCP section 3.3.4.4</i>). All other geographies: Submit to Ethics Committee per local reporting requirement.

Sponsor submit to:	
Regulatory authorities	All geographies: Submit to regulatory authority per local reporting requirement.
Ethics Committee	All geographies: Submit to regulatory authority per local reporting requirement.

9.4 Product Complaints / Vigilance Reporting

All devices used in this study will be market released at study start. Therefore, product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements. In case the adverse event is related to a non-Medtronic market released device used during the study, post-market surveillance is also applicable and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market-released products.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1 rev6)

Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1 rev6)

It is the responsibility of the investigator and the clinical study team to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
A serious deterioration in the state of health includes:
 - Life-threatening illness or injury.
 - Permanent impairment of a body function or permanent damage to a body structure.
 - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

9.5 Subject Death

9.5.1 Death data collection

All subject deaths must be reported by the investigator to Medtronic on a Subject Death form immediately or in a timely manner per geography requirements after the investigator first learns of the death. The SAE leading to death should also be reported on an Adverse Event Form. There should only be one AE form with an outcome of death.

In the event of a subject's death, the implanted system should be explanted and returned to Medtronic (or per other manufacturer's procedure) for analysis whenever possible. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible. Save a copy of the device interrogation on a USB flash drive or other removable electronic media. Device data should be sent to Medtronic using the secure, electronic Clinical Transfer utility.
- Make the interrogation file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

For ICD systems, the VT and VF detection capabilities must be disabled to avoid inadvertent shocks. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records when obtainable should be sent to the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)

- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

9.5.2 Death classification and reporting

Sufficient information will be required in order to properly classify the subject’s death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Cardiac Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death

Table 12: Subject death classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The Clinical Events Committee (CEC) will review deaths and provide a final adjudication of the classification of death.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

9.6 Clinical Events Committee (CEC) review

At regular intervals, an independent CEC will review and adjudicate all CIED system related (including TYRX envelope related), CIED procedure related, and all CIED infection related adverse events as classified by the investigator or Medtronic. In addition the CEC will review and adjudicate the classification of all deaths as well as the serious AEs leading to death.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. The details of the CEC procedures, including how potential events for adjudication are identified, will be provided in a separate CEC Charter. CEC adjudications will be used for data analysis.

The CEC members will not be made aware of subjects’ randomization assignment and/or other data or procedures that may influence their decision whenever possible. However, in certain instances (e.g. events related to the TYRX envelope), the CEC members may become aware of the subjects treatment assignment.

Medtronic personnel may assist in facilitating CEC meetings but will be non-voting members.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification and supportive documentation (when available). The CEC will review applicable definitions, and determine final classifications for all adjudication parameters. For adverse events related to the CIED system, CIED procedure, classification includes relatedness and complication or observation. Additionally, the CEC will provide an adjudication of the cardiac classifications for all reported deaths. The CEC will also review each CIED infection and determine, if each CIED infection meets the primary endpoint definition.

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>

10 RISK ANALYSIS

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

All devices used in the WRAP-IT study will be commercially released and used in accordance with their approved labeling. The safety and clinical performance of these devices have been demonstrated through previous pre-clinical testing and previous clinical studies.

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for intention to treat analysis, but the investigator will avoid any procedures that may be determined harmful.

The risks must be continuously monitored, assessed and documented by the investigator.

A summary of the risk analysis and risk assessment will be listed in the Investigator Brochure.

10.1 Potential Risks and Side Effects

The potential risks and side effects associated with the study can be found in the IFL (refer to Appendix J) and the foreseeable adverse event list (Appendix G) which are consistent with market-released IPG/CRT-P, ICD/CRT-D systems and TYRX™ Absorbable Antibacterial Envelopes (henceforth referred to as TYRX envelopes). Additional risks for participating in this study may include the following:

- In the event that a LSE is suspected and a Holter is required, the electrodes used with the Holter recorder might cause mild skin discomfort or irritation or some skin discomfort following electrode removal.

10.2 Potential Benefits

The potential benefits of having the TYRX envelope include holding the CIED generator securely in the pocket providing a stable environment and reducing the risk of CIED infection. In addition, subjects enrolled in the study may have additional contact with their physicians or other medical care staff beyond their normal standard of care visits, which may provide benefit from a patient care perspective. The information gained from this study could result in the improved management of other methods to reducing CIED infections. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

10.3 Risk-to-Benefit Analysis

The potential risks associated with the commercially available IPG/CRT-P, ICD/CRT-D and TYRX envelope implant were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan. Medtronic

has also attempted to minimize risk to subjects implementing a Data Monitoring Committee to review safety issues as part of the study. In addition, investigators will be actively involved in the implantation and follow-up of the subjects. Risks will be minimized by careful assessment of each subject prior to, during, and after implant. Medtronic has further minimized the possibility of risks by product testing applicable to all commercially available devices prior to their use in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling. After implantation, subjects in this clinical study will be followed at regular intervals to monitor the condition of the implanted system and the battery. At each CIP-required follow-up, in all subjects, the investigator must interrogate the IPG/CRT-P, ICD/CRT-D device to verify appropriate IPG/CRT-P, ICD/CRT-D function and to assess any adverse events.

Taking the risk mitigation and risk minimization into account, the potential benefits outweigh the potential risks for patients participating in this study.

11 PLANNED STUDY CLOSURE, EARLY TERMINATION OF STUDY OR STUDY SUSPENSION

11.1 Planned study closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing Ethics Committee oversight is required until the overall study closure process is complete. Upon study closure, patients should be managed and followed per physician discretion

11.2 Early termination or suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site.

11.2.1 Study-wide termination or suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Recommendation of early termination by the Data Monitoring Committee (DMC) based on interim analyses.
- Technical issues during the manufacturing process

11.2.2 Investigator/site termination or suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Committee approval or annual renewal of the study
- Persistent non-compliance to the clinical study (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

11.3 Procedures for termination or suspension

11.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(ies) where required.
- In the case of study termination or suspension for reasons other than a temporary Ethics Committee/Head of Medical Institution approval lapse, the investigator will promptly inform the Ethics Committee.
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic.
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

11.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension.
- The investigator will promptly inform the institution (where required per regulatory requirements).
- The investigator will promptly inform the Ethics Committee.
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare.

11.3.3 Ethics committee-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days.
- Subject enrollment must stop until the suspension is lifted.
- Subjects already enrolled should continue to be followed in accordance with Ethics Committee/ policy or its determination that an overriding safety concern or ethical issue is involved.
- The investigator will inform his/her institution (where required per local requirements).
- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension.

12 STATISTICAL METHODS AND DATA ANALYSIS

12.1 General Considerations

Medtronic employees or their designated representatives will perform all statistical analysis. The lead study statistician will be blinded to all interim analyses in which the treatment groups are compared. An Intention-to-Treat (ITT) analysis will be performed and will serve as the primary analysis for all objectives in this study unless otherwise specified. The ITT analysis cohort will include all randomized subjects regardless of treatment received.

Additionally, a separate Statistical Analysis Plan (SAP) will be developed to further describe statistical methods, pre-specified data handling rules, and pre-specified analyses that will be included in the final study report and primary study publication(s). However, additional exploratory analyses of the data may be conducted as deemed appropriate.

The SAP for this study will also include information regarding:

- Procedures for reporting any deviation(s) from the original statistical plan with justification
- Procedures that take into account all the data with justification (also described below)
- The treatment of missing, unused, unauthentic or spurious data, including drop-outs and withdrawals with justification (also described below)

The study will be considered successful if the primary objective is met.

12.2 Analysis Cohorts

Intention-to-Treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified.

As Treated (AT): The AT cohort includes subjects in the ITT cohort but analyzes subjects using the treatment they actually received. For subjects with a TYRX envelope this means the TYRX envelope remained in the pocket following pocket closure.

modified As Treated (mAT): The mAT cohort includes all subjects and follow-up time in the AT cohort that were successfully implanted with a CIED system (including the TYRX envelope if subject had a successfully placed TYRX envelope) up until the point where a CIED modification (i.e. pocket revision) was required. Thus, subjects with a system modification for reasons other than device infection will be considered censored at the time of the system modification.

12.3 Interim Analysis and Type 1 Error Control

The study has up to two planned analyses of the primary objective. The study may be considered successful at the first analysis in which the primary objective is met.

The first analysis will occur when approximately 50% of the total follow-up within 12-months of randomization occurs; based on enrollment projections described below this is defined as the point where 3200 randomized subjects complete the 6-month post-procedure visit. The purpose of this first analysis is two-fold:

- (1) To assess whether the study's primary objective has been met. If the DMC indicates that the study has met its objective, the study may continue to enroll and follow subjects to study the effect of the TYRX envelope on long-term CIED infections as well as accumulate LSEs. However, subjects enrolling following review of the interim analysis may no longer be randomized upon recommendation of the DMC if the TYRX envelope is found to have a clear benefit.
- (2) To assess whether the study may end earlier than planned for futility.

The timing of the interim analysis was selected so that sufficient data is collected to contribute to the interim analysis before decisions that impact the study are made. The Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) is used to control the overall alpha level at 5% (two-sided; 2.5% one-sided in the direction favorable to the TYRX envelope). This function spends the alpha at a level analogous to the O'Brien-Fleming boundary. The boundary condition at the interim analysis will be based on the information fraction at the interim analysis and computed by dividing the accrued number of major CIED infections observed at the interim analysis by the total number of major CIED infections anticipated at the final analysis. Assuming the information fraction at the interim analysis is 50%, the boundary condition at the interim analysis is 0.003 (2.75 on the Z-scale or 0.006 on the two-sided p-value scale) and is purposely low to allow early claims of study success only when the TYRX envelope is highly effective. At the final analysis, the boundary condition is 0.0238 (1.98 on the Z-scale or 0.0476 on the two-sided p-value scale) when the information fraction is 50% at the interim analysis. Since the analytical methods for the secondary objectives also utilize survival analysis methods, the same alpha spending function will be used to compute the success boundaries for the secondary objectives.

If the primary objective of the study is met, the secondary objectives will be tested using the Holm procedure to protect the overall type I error rate of the study and allow statistically valid claims of significance. Specifically, at analysis k ($k=1,2$), the ordered hypotheses $H_{(1k)}, H_{(2k)}, H_{(3k)}$ corresponding to the ordered p-values $p_{(1k)}, p_{(2k)}, p_{(3k)}$ of the secondary objectives will be tested based off the sequentially rejective algorithm. The hypothesis $H_{(1k)}$ is rejected if $p_{(1k)} \leq \alpha_k/3$. Further, $H_{(jk)}$ is rejected at the j^{th} step if $p_{(jk)} \leq \alpha_k/(3 - j + 1)$. Otherwise, $H_{(jk)}, \dots, H_{(3k)}$ are retained and the algorithm terminates.

To help assess whether the study may end earlier than planned for futility, stochastic curtailment methods will be used to calculate the futility index for the primary objective. The futility index ($1-P_1$, where P_1 is the predictive power observed at the interim analysis) is based on predictive power as computed using equation 10.6 in Jennison and Turnbull (2000) and is defined as the probability the study will not meet its primary objective at the final analysis ⁸² time point based on data accrued at the time of the interim analysis. Although non-binding, a futility index greater than 0.9 at the interim analysis provides strong evidence that the study will not achieve its primary objective if the study were to continue to its full sample size and follow-up.

12.4 General Summaries

12.4.1 Description of Baseline Variables

Standard baseline and relevant medical history will be collected on the eCRFs for all enrolled subjects. Baseline and medical history variables to be summarized include, but are not limited to: age, sex, race, device type (CRT-D, ICD, CRT-P, and IPG), number of previous CIED devices, NYHA class, arrhythmia history, and baseline medication use.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Summaries of baseline information will be summarized for all randomized subjects. The TYRX envelope and control groups will be compared using T-tests for continuous variables and the Chi-square test for categorical variables to quantify any imbalance in treatment groups.

12.5 Primary Objective: Major CIED Infection Rate through 12-months

12.5.1 Objective

The primary study objective is to compare the rate of major CIED infections through 12-months post-procedure between the TYRX envelope group and the control group (no TYRX envelope).

12.5.2 Hypothesis

The primary study objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_c(t)$ for all $t \leq 12$ months (365 days), versus

$H_a: \lambda_T(t) \neq \lambda_c(t)$ for some $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for major CIED infection in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for major CIED infection in the control group.

12.5.3 Major CIED Infection Definition

Major CIED infection is defined in section 5.2.1.

12.5.4 Sample Size Determination

Background

The reported prevalence rate of CIED infection varies widely in the literature and is dependent on the nature of data collection (retrospective vs prospective, single center vs multi-center), CIED infection definition, and population studied. The REPLACE study prospectively evaluated CIED infection requiring system removal or intravenous antibiotics in 1744 subjects undergoing a device replacement or upgrade. The infection rate at 6-months post-procedure for subjects receiving a device replacement was 1.4% and 1.1% for those subjects undergoing a device upgrade.¹⁰

Analysis of 103,020 device implant claims from Medicare evaluated for Medtronic by Truven Analytics suggested that subsequent invasive procedures related to device infection occurred at a rate of 4.0% for CRT-D, 3.9% for ICDs, and 2.6% for pacemakers through 12-months. The 12-month CIED infection rate associated with replacement devices was 4.1% for CRT-D, 5.4% for ICDs, and 3.4% for pacemakers with 12-month

infection rates associated with initial device implants ranging from 4.0% in CRT-Ds to 2.2% in pacemakers. However, examination of CIED infections reported in Medtronic studies, suggests that the Medicare claims data may overestimate the CIED infection rate that may be observed in clinical trials for initial implants by at least 50% (Table 14).

Table 14: 12-Month Infection Rates for Initial Implants by Device Type and Data Source

Device	Data Source	
	Medicare Claims Data 12-Month CIED Infection Rate	Medtronic Studies (12-month CIED Infection Rate (95% CI))
CRT-D	4.1%	2.0% (1.2% - 3.4%) ¹
ICD	3.0%	1.5% (0.3% - 6.7%) ²
Pacemaker	2.2%	1.2% (0.8% - 1.7%) ³

¹Based on 753 subjects with an attempted CRT-D implant in the REVERSE and BLOCK-HF studies.

²Based on 246 subjects from the Model 6947, 6948, and 6949 RV defibrillation lead studies

³Based on 2799 subjects from the 3830, 4074, 5076, Advisa MRI, EnRhythm, EnRhythm MRI, and SAVEPACE studies.

Based on the assumption that the Medicare claims data may overestimate the actual CIED infection rate that may be observed in a clinical trial, it is hypothesized that the 12-month infection rate for initial CRT-D implants, replacement (or upgrade) CRT-D implants, and replacement (or upgrade) ICD implants is 2.4% and is 0.6% for replacement pacemaker implants. Since low power replacement procedures (i.e. pacemaker and CRT-P replacement procedures) will be capped at 25% of the total sample size, an overall 12-month CIED infection rate for the control group is assumed to be 2% for sample size calculation purposes.

Retrospective evidence from the COMMAND study demonstrated that in 624 subjects consecutively implanted with the TYRX envelope the CIED infection rate was 0.48% and ranged from 0% during initial implant procedures and 1.05% during ICD/CRT-D replacement/revision procedures.⁵⁶ Additionally, recently published data from Mittal, et. al showed that the CIED infection rate was 1.1% in 275 subjects that received the TYRX envelope compared to 3.6% in 275 propensity matched control subjects over a 6-month period across both low power and high power devices.⁷³ Finally, early evidence from the CITADEL/CENTURION studies suggests that CIED infection rate among a cohort of 1000 ICD/CRT-D subjects receiving the TYRX envelope is 0.2% at 6-months post-replacement/upgrade; a 9-fold decrease compared to published controls at 6-months. Based on this experience, it is assumed that the TYRX envelope will reduce the risk of CIED infection by 50% through 12-months post-procedure.

Sample Size Calculation

The sample size is derived based on the following assumptions:

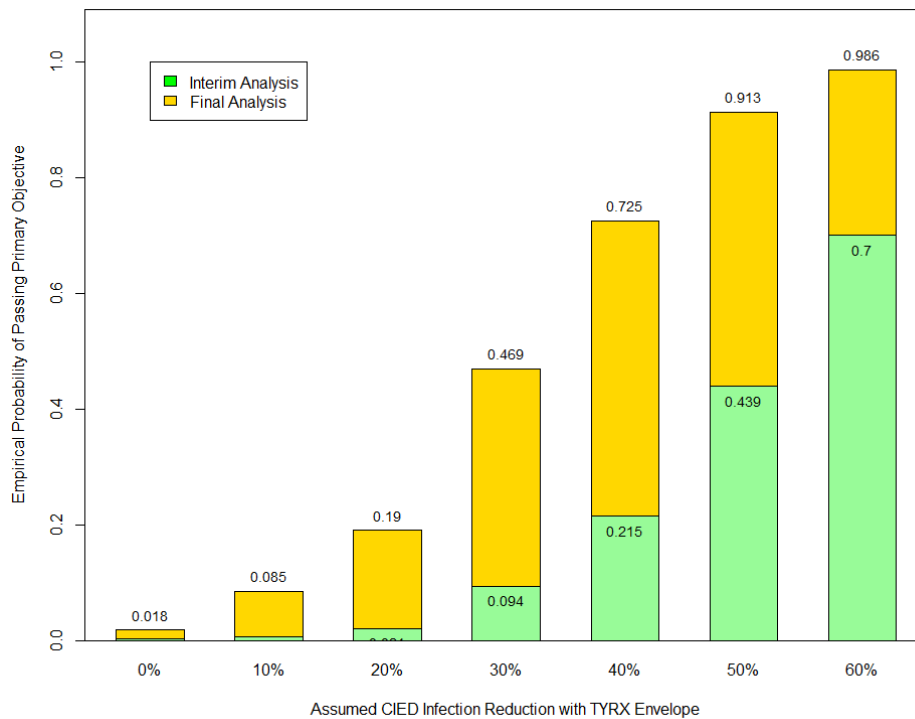
1. One-to-one randomization to the TYRX envelope or control group
2. Power to test the primary objective is at least 90%
3. One interim analysis and final analysis
4. The interim analysis will occur when approximately 50% of the statistical information has been accrued
5. One-sided alpha level of 2.5%

6. Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) which approximates O'Brien-Fleming boundaries
7. Assumed control CIED infection rate of 2% at 12-months
 - a. 2.4% for high power (CRT-D/ICD) devices
 - b. 0.6% for low power (pacemaker/CRT-P) devices
 - c. Low power devices are capped at 25% of the required sample size
8. TYRX envelope assumed to reduce the control infection rate by 50%
9. Non-binding futility assessment based on stochastic curtailment at the interim analysis
10. 15% annualized attrition rate that is independent of treatment group and infection status

The method of Lakatos (1988) as implemented in the POWER procedure of SAS v9.2, indicated 6,988 randomized subjects (3,494 randomized to each group) are required to test the primary objective based on the assumptions described above. Thus, up to 7,764 subjects may be enrolled to allow for up to a 10% discontinuation rate between enrollment (i.e. subject consent) and randomization.¹⁷

A simulation study was performed to confirm the sample size calculation. In addition to the sample size assumptions described above, the simulation assumed that 50% of CIED infections occur within the first month of device procedure. Simulations were performed when the CIED infection risk reduction associated with the TYRX envelope ranged from 0% (null case) to 60%. Figure 1 confirms the sample size calculation and demonstrates that the type I error rate is well controlled.

Figure 1: Empirical Power to Test the Primary Objective (n=6,988)



12.5.5 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the primary endpoint. The primary method to be used to test the primary objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from procedure (or randomization if the subject was randomized but no procedure attempt) to: (1) onset date of a subject’s first CIED infection meeting the primary endpoint, (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of 12-month visit (if completed), (5) date of last follow-up, or (6) 365 days post-procedure. Subjects not meeting the primary endpoint during the follow-up period will be considered censored. Based on this statistical test, it will be claimed that the TYRX envelope reduces major CIED infection if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function.

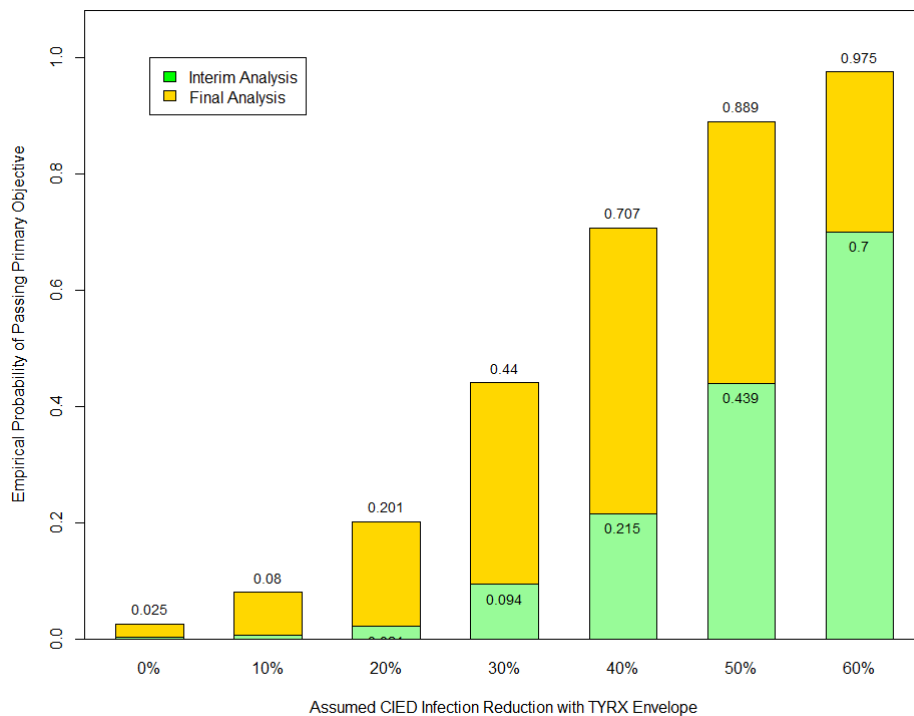
12.5.6 Determination of subjects for analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope the AT or mAT cohorts as described above.

12.5.7 Pre-specified Subgroup analyses

The primary objective will be evaluated separately within high power (CRT-D, ICD) devices and low power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. Due to the large number of high power devices in this study (n=5,242), combined with the higher assumed CIED infection rate, the study has 89% power to test the primary objective within subjects implanted with a CRT-D or ICD. Figure 2 displays the power of the study to evaluate the primary objective among subjects implanted with high power devices as evaluated in the simulation study described above. Cox regression models will be used to evaluate the homogeneity of the treatment effect across device type by including an interaction term for device type and treatment.

Figure 2: Empirical Power to Test the Primary Objective in Subjects Receiving CRT-D or ICD Devices (n=5,242)



12.5.8 Missing data

The primary analysis cohort will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a CIED infection meeting the primary endpoint. Thus, if missing data becomes an issue, sensitivity analyses will be conducted to assess the sensitivity of the primary results to the missing data.

12.6 Secondary Objectives

The following secondary objectives will be evaluated to gain additional information about the performance of the TYRX envelope. The type I error is controlled for the secondary objectives as described in section 12.3.

Provided the primary objective is met, then the secondary objectives will be assessed using the Holm multiple comparisons procedure as described in section 12.3.

12.6.1 Secondary Objective #1: Procedure- or System-related complications through 12-months

12.6.1.1 Objective

Confirm that the TYRX envelope does not increase the CIED procedure-related or system-related complication rate through 12-months post-procedure.

12.6.1.2 Hypothesis

The first secondary objective will be tested with the following non-inferiority hypothesis:

$H_0: \lambda_T(t)/\lambda_c(t) \geq 1.33$ for $t \leq 12$ months (365 days), versus
 $H_a: \lambda_T(t)/\lambda_c(t) < 1.33$ for $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for CIED system or procedure related complications in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for CIED system related complications in the control group. Rejecting the null hypothesis would indicate that the TYRX envelope does not increase the CIED system or procedure related complication rate by more than 33% on a relative scale or 4.4% on a linear scale when the underlying CIED system or procedure complication freedom rate at 12-months is 85%.

12.6.1.3 CIED system or procedure related complications

A CIED system related complication is defined as an adverse event that meets the complication definition as defined in Table 9 and is considered as related to one of the implanted CIED system components (i.e. device, RV lead, RA lead, LV lead, other lead, or the TYRX envelope).

A CIED procedure related complication is defined as an adverse event that meets the complication definition as defined in Table 9 and is considered related to the CIED procedure (i.e. replacement/upgrade/new implant/revision) or a system modification including the TYRX envelope (if applicable).

12.6.1.4 Power to test the objective

Background

Table 15 displays the procedure- or system-related complication rates from several Medtronic and non-Medtronic sponsored studies. These data indicate that complications related to the implanted system (i.e. device and leads) or procedure range from 4.0% to 24.7% depending on complication definition, devices studied, and study population. Based on these data it appears reasonable based on the mix of devices and population under investigation in the WRAP-IT study that the underlying system or procedure complication free rate could range from 80% to 90% at 12-months post-procedure.

Table 15: System or Procedure-Related Complications Reported Previous Studies

Study	Devices Studied	Population	Time Frame	Complication Rate (95% CI)
Gould et. al 2008 ¹	ICD (n=451)	Replacements	12-months	9.1% (NR)
REPLACE ²	IPG (n=515) ICD (n=327) CRT-D (n=175) CRT-P (n=14)	Replacements	6-months	4.0% (2.9%-5.4%)
REPLACE	IPG (n=329) ICD (n=320) CRT-D (n=49) CRT-P (n=15)	Upgrades	6-months	15.3% (12.7% - 18.1%)
BLOCK-HF	CRT-D (n=230)	New Implants	12-months	22.9% (18.0% - 29.0%)
BLOCK-HF	CRT-P (n=531)	New Implants	12-months	17.7% (14.7% - 21.3%)
REVERSE	CRT-D (n=523)	New Implants	12-months	17.0% (14.0% - 20.5%)
REVERSE	CRT-P (n=104)	New Implants	12-months	24.7% (17.5% - 34.4%)
4074 Study	IPG (n=132)	New Implants	6-months	13.9% (9.0% - 21.1%)
EnRhythm MRI ³	IPG (n=469)	New Implants	12-months	11.3% (8.8% - 14.6%)
Advisa MRI ³	IPG (n=269)	New Implants	6-months	9.2% (6.3% - 13.4%)

¹Gould et. al. 2008. Heart Rhythm 5: 1675-1681. Major complication defined as post-operative death, nonfatal MI, cardiogenic shock, or event requiring reoperation.

²Poole et. al. 2010. Circulation 122:1553-1561. Major complications defined as an event defined in Table 1 of the manuscript. In general major complications required invasive intervention.

³Does not include system complications related to the RA lead only.

Power Calculation

Since the primary objective of the study dictates the sample size for the study, the power to test this secondary objective under several scenarios was determined based on the method of Lakatos ⁷⁷ as implemented in PASS 2008. The following assumptions were made in the power calculation:

1. Sample size of 6,988 subjects randomized 1:1 to the TYRX envelope or control group
2. One interim analysis and final analysis
3. The interim analysis will occur when approximately 50% of the follow-up is accrued
4. One-sided alpha level of 2.5%
5. Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) which approximates O'Brien-Fleming boundaries and means the final test will be conducted at a one-sided alpha-level of 0.0238 which is analogous to a two-sided alpha level of 0.0476.
6. 15% annualized attrition rate that is independent of treatment group and system related complication
7. 12-month system or procedure related complication rate in the control group could range from 10% to 20%
8. The TYRX envelope has no effect on the system or procedure related complication rate
9. Non-inferiority margin of 33% on a relative scale or 4.4% on a linear scale when the underlying CIED system complication freedom rate at 12-months is 85%

Table 16 indicates that the statistical power to test the non-inferiority hypothesis associated with secondary objective #1 is greater than 94% based on the assumptions above across a range of plausible control group event rates.

Table 16: Power to Test Secondary Objective #1 with Sample Size of 6,988 Subjects

12-month system-related Complication Free Rate	Control Group Hazard Rate	Non-inferiority Margin (Relative Scale)	Non-inferiority Margin (Linear Scale) ¹	Power
90%	0.1054	1.33	3.1%	94.9%
88%	0.1278		3.6%	97.6%
86%	0.1508		4.2%	98.9%
85%	0.1625		4.4%	99.3%
84%	0.1744		4.7%	99.5%
82%	0.1985		5.2%	99.8%
80%	0.2231		5.7%	99.9%

¹The non-inferiority margin on the linear scale is defined as the difference in the survival curves for the event rate at 12-months post-randomization between the control group and the TYRX™ Absorbable Antibacterial Envelope group.

12.6.1.5 Analysis Methods

All potential adverse events potentially related to the implanted system (i.e. device, leads) the TYRX envelope, or the CIED replacement/upgrade/implant or system modification procedure will be reported on the eCRFs as they occur. The CEC will adjudicate each reported adverse event for its relationship to the CIED system and CIED procedure. Additionally, the CEC will classify each CIED system related or procedure related adverse event as a complication or observation. Days of follow-up for each subject will be set to the minimum of days from procedure (or randomization if a subject was randomized but not implanted) to: (1) onset date of a subject's first CIED system related or procedure related complication (including the TYRX envelope where applicable), (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of 12-month visit (if completed), (5) date of last follow-up, or (6) 365 days post-procedure. Subjects not having a CIED system related or procedure related complication during the follow-up period will be considered censored.

The effect of the TYRX envelope on the rate of CIED system or procedure related complications will be tested using a Cox proportional hazards regression model stratified by device type (low power versus high power) containing an indicator term for treatment group. The observed hazard ratio from the Cox model will be compared to the non-inferiority margin of 1.33. The null hypothesis will be rejected in favor of the alternative and the TYRX envelope will be considered non-inferior to the control group if the p-value computed from the non-inferiority test is less than the type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons.

12.6.1.6 Determination of subjects for analysis

Since non-inferiority tests based on intention-to-treat principles may be anti-conservative, the results of the non-inferiority test will be reported for both the ITT and AT cohorts as recently suggested.⁷⁸ However, statistical inference for this objective will be based on the AT cohort. All randomized subjects and all follow-up from randomized subjects is included in the ITT cohort regardless of treatment received. For the AT cohort, all follow-

up from all subjects will be included, but the analysis will be based on the treatment the subject actually received.

12.6.1.7 Pre-specified Subgroup analyses

The TYRX envelope to control group hazard ratio along with its 95% confidence interval will be displayed separately within high power (CRT-D, ICD) devices and low power (IPG, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types.

12.6.1.8 Missing Data

The analysis cohorts will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a CIED system or procedure related complication. Thus, if missing data becomes an issue, sensitivity analyses will be conducted to assess the sensitivity of the results to the missing data.

12.6.2 Secondary Objective #2: Major CIED Infection Rate through Study Duration

12.6.2.1 Objective

Compare the major CIED infection rate during the entire follow-up between the TYRX envelope group and the control group.

12.6.2.2 Hypothesis

The second secondary objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_c(t)$ for all $t \leq T$, versus

$H_a: \lambda_T(t) \neq \lambda_c(t)$ for some $t \leq T$

where $\lambda_T(t)$ is the hazard function for major CIED infection in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for major CIED infection in the control group during the entire follow-up period.

12.6.2.3 Major CIED Infection Definition

Major CIED infection is defined in section 5.2.1.

12.6.2.4 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the major CIED infection definition. The primary method to be used to test this objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an

independent variable. Days of follow-up for each subject will be set to the minimum of days from procedure (or randomization if a subject was randomized but not implanted) to: (1) onset date of a subject's first CIED infection meeting the primary endpoint, (2) study exit date (if exited), (3) date of death (if death occurs), or, (5) date of last follow-up. Subjects not having a major CIED infection during the follow-up period will be considered censored at their last follow-up day. Based on this statistical test, it will be claimed that the TYRX envelope reduces major CIED infection during the entire study period if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons.

12.6.2.5 Determination of subjects for analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope in the AT or mAT cohorts as described above. ⁷⁸

12.6.2.6 Pre-specified Subgroup analyses

The TYRX envelope to control group hazard ratio along with its 95% confidence interval will be displayed separately within high power (CRT-D, ICD) devices and low power (IPG, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. Cox regression models will be used to evaluate the homogeneity of the treatment effect across device type.

12.6.2.7 Missing Data

The primary analysis cohort for this objective will include all follow-up from all randomized subjects through the end of the study or visit cutoff for the interim analysis (i.e. Intention-to-Treat principle). However, missing data could arise if a randomized subject exits the study or dies prior to the end of the study (or visit cutoff) without experiencing a major CIED infection. Thus, if missing data becomes an issue, sensitivity analyses will be conducted to assess the sensitivity of the results to the missing data.

12.6.3 Secondary Objective #3: Major and Minor CIED Infection Rate through 12-months

12.6.3.1 Objective

Compare the rate of major and minor CIED infections through 12-months post-procedure between the TYRX envelope group and the control group.

12.6.3.2 Hypothesis

The third secondary objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_c(t)$ for all $t \leq 12$ months (365 days), versus
 $H_a: \lambda_T(t) \neq \lambda_c(t)$ for some $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for major and minor CIED infection in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for major and minor CIED infection in the control group.

12.6.3.3 Major and Minor CIED Infection Definition

Major and minor CIED infections are defined in section 5.2.1.

12.6.3.4 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the major CIED infection definition. Those infections related to the CIED that do not meet the major CIED infection will be considered minor CIED infections. The primary method to be used to test the primary objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from procedure (or randomization if a subject is randomized but not implanted) to: (1) onset date of a subject's first major or minor CIED infection, (2) study exit date (if exited), (3) date of death (if death occurs), (5) date of last follow-up, or (6) 365 days post-procedure. Subjects not having a major or minor CIED infection during the follow-up period will be considered censored. Based on this statistical test, it will be claimed that the TYRX envelope reduces major or minor CIED infection if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons.

12.6.3.5 Determination of subjects for analysis

All randomized subjects will be included in the analysis of this secondary objective regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope in the AT or mAT cohorts as described above.

12.6.3.6 Pre-specified Subgroup analyses

The TYRX envelope to control group hazard ratio along with its 95% confidence interval will be displayed separately within high power (CRT-D, ICD) devices and low power (IPG, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. Cox regression models will be used to evaluate the homogeneity of the treatment effect across device type.

12.6.3.7 Missing Data

The primary analysis cohort for this objective will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization,

whichever occurs first. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a major or minor CIED infection. Thus, if missing data becomes an issue, sensitivity analyses will be conducted to assess the sensitivity of the primary results to the missing data.

12.7 Ancillary Objectives

The following ancillary objectives are intended to gain additional information about the performance of the TYRX envelope. The type I error rate is not controlled for the ancillary objectives.

12.7.1 Ancillary Objective #1: Mortality

Objective

To compare all-cause mortality rates between the TYRX envelope group and the control group.

Endpoint

Death for any cause

Hypothesis

This ancillary objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_c(t)$ for all $t \leq T$, versus

$H_a: \lambda_T(t) \neq \lambda_c(t)$ for some $t \leq T$

where $\lambda_T(t)$ is the hazard function for death for any cause in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for death any cause in the control group during the entire follow-up period.

Analysis Methods

The primary method to be used to evaluate the hypothesis above will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from procedure (or randomization if a subject was randomized but not implanted) to the (1) date of death or (2) last date subject was known to be alive. Subjects alive at their last follow-up day will be censored.. A p-value less than 0.05 will be considered statistically significant.

Determination of Subjects for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

12.7.2 Ancillary Objective #2: CIED procedure success rate

Objective

Evaluate the CIED procedure success rate in the TYRX envelope group and the control group

Analysis Methods

Information related to the CIED procedure (i.e. initial implant or index replacement/upgrade or index system revision) will be collected on the procedure eCRF. A procedure attempt is defined as any CIED procedure where the device pocket is opened or venous access was gained (i.e. skin was cut). A successful procedure is defined as an implant attempt where the device is successfully connected to the system's leads and the CIED system remains in the body and the device pocket is closed. Additionally, for those subjects randomized to the TYRX envelope group, the TYRX envelope must also remain in the device pocket following pocket closure to qualify as a successful CIED procedure. The CIED procedure success rate will be defined as the number of subjects with a successful CIED procedure divided by the number of subjects with a CIED procedure attempt. Fisher's exact test will be used to compare the procedure success rate between the TYRX envelope group and the control group.

Determination of Data for Analysis

Data from all randomized subjects with a CIED procedure attempt will be included in the analysis.

12.7.3 Ancillary Objective #3: Summarize adverse events

Objective

To summarize adverse events by treatment group

Analysis Methods

Subjects will be queried for AEs at all scheduled and unscheduled visits. All AEs potentially related to the CIED system, CIED implant or system modification procedure, and all SAEs regardless of their relationship to the CIED system or CIED procedure (including the TYRX envelope if applicable) will be collected. Medtronic safety specialists will ensure that at a minimum all AEs that are potentially related to the CIED system (including the TYRX envelope), or CIED procedure, or death are classified by the CEC. Summary tables will be compiled categorizing the AEs with respect to procedure relatedness, CIED relatedness (including CIED component), and TYRX envelope relatedness. For events classified by the CEC, the CEC classification will be used in the analysis. In cases where only the investigator classifies the event, the investigator's classification will be used. In addition, the number of events and number of subjects with events by MedDRA term will be displayed. Additionally, the nominal p-value from the log-rank test will be used to identify AEs occurring on or after a CIED procedure attempt by MedDRA preferred term that may differ between treatment groups. This test does not protect the type I error, but may help identify specific AEs that differ between randomized treatment group for further evaluation.

Determination of Data for Analysis

All adverse events collected during the study will be included in this analysis.

12.7.4 Ancillary Objective #4: Predictors of CIED infection

Objective

To identify predictors of major CIED infection

Analysis Methods

Subject demographics and medical history including previous device history will be collected at baseline. CIED procedure related variables such as antibiotic prophylaxis, surgical site preparation, procedure duration, device type, and number of leads will be collected for each CIED procedure. Additionally, device characteristics such as impedance, optivol fluid status, and heart rate variability will be collected via device interrogations at each follow-up visit. Cox regression modeling will be employed using subjects in the control group to develop a major CIED infection model using a candidate set of predictors. The number of degrees of freedom available and hence the number of candidate predictors available for modelling will be determined by the number of major CIED infections in the control group.

Determination of Data for Analysis

All subjects randomized to the control group with a CIED procedure attempt who do not receive the TYRX envelope at CIED procedure.

12.7.5 Ancillary Objective #5: Quality of Life

Objective

Summarize quality of life.

Analysis Methods

Subjects will be asked to complete the EQ-5D questionnaires at baseline and at the 12-month visit (or study exit if the subject exits the study for reasons other than lost to follow-up prior to completing the 12-month visit). Additionally, subjects with a CIED infection will be asked to complete the EQ-5D within two weeks following their CIED infection diagnosis and at 1-month, 3-months, and 6-months post-CIED infection diagnosis. Descriptive statistics will be used to summarize the change in EQ-5D scores from baseline to the 12-month visit by randomized treatment group. Additionally, the changes in EQ-5D between CIED infection and post-CIED infection will be computed using summary statistics for all subjects with a major CIED infection as classified by the CEC.

Determination of Data for Analysis

Completed EQ-5D questionnaires from all randomized subjects will be used to describe the changes in EQ-5D score from baseline. All completed EQ-5D questionnaires following an adjudicated CIED infection will be used to summarize the change in EQ-5D score from baseline following CIED infection.

12.7.6 Ancillary Objective #6: Healthcare System Cost Effectiveness

Objective

To assess the cost-effectiveness of the TYRX envelope.

Analysis Methods

Health care utilizations (HCUs) related to suspected CIED infection will be collected on the eCRFs. HCUs related to CIED infection include all hospitalizations, emergency department visits, urgent care, or unscheduled follow-up visits associated with the

suspected CIED infection regardless of location of care. Summary statistics will be used to quantify HCU related to CIED infection by treatment group.

Additionally, the cost incurred from each major CIED infection will be based on the actions taken to address each major CIED infection. The total cost of major CIED infections observed in the study will be compared to the total cost incurred by adding the TYRX envelope to the CIED procedure. Economic models will be employed to quantify the cost savings and/or cost-effectiveness of the TYRX envelope. The decision-analytic framework of any potential economic model will be detailed in the health economics analysis plan.

Note: While cost-effectiveness is an important objective of the WRAP-IT study, cost-effectiveness data will be analyzed separately from those included in the WRAP-IT study report and primary manuscript.

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13 DATA AND QUALITY MANAGEMENT

Data will be collected using an electronic data management system for clinical studies. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred to and processed by Medtronic or a third party designated by Medtronic but solely in a key-coded form, unless it's impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier, such as X-rays. In the case that de-identifying is impossible or involves a disproportionate effort, files containing personal data of patients shall only be made accessible to authorized persons (secured role-based access).

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include, but are not limited to, worksheets, patient medical records, lab results, ECGs, programmer printouts, and interrogation files, must be created and maintained by the investigational site team. In some cases, the data reported in the eCRFs may be considered source, as long as there is evidence of the visit in the subject's record. The electronic case report form (eCRF) may serve as the primary source for the following data points:

- Enrollment Notification
 - Site assigned patient reference
- Baseline
 - Administrative Information
 - Cardiac Disease Classification
- Adverse Event eCRF
 - Date study center became aware of event
 - Relatedness of adverse event
- Device Deficiency eCRF
 - Date study center became aware of event
- Subject Death
 - Date study center became aware of death
 - Relatedness of death
 - System Explant Information
- System Modification
 - Justification for explanted product not being returned to Medtronic.
- Deviations

- Reason for deviation

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. When copies or print-outs of the source documents are made, the investigational site study team must sign and date any copies or printouts of original source documents with a statement that this is complete and true reproduction of the original source document.

Device data from CareLink[®] transmissions will be uploaded to secure servers and made accessible to the study team. Device interrogation files collected via electronic media at office visits will be sent to Medtronic. Upon receipt via transmission or electronic media, device data will be maintained within secure databases and retrieved for analysis and reporting.

14 WARRANTY/INSURANCE INFORMATION

14.1 Warranty

There is no warranty associated with the TYRX™ Absorbable Antibacterial Envelope.

14.2 Insurance (EMEA)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

14.3 Insurance (ASEAN (Singapore and Malaysia))

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

14.4 Insurance (New Zealand)

Medtronic Australasia Pty Ltd is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Study insurance statement/certificate will be provided to the Ethics Committee.

14.5 Insurance (Greater China (Hong Kong))

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

14.6 Insurance (India)

India Medtronic Pvt. Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Study insurance statement/certificate will be provided to the Ethics Committee.

14.7 Insurance (Latin America)

Medtronic Latin America HQ is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

15 MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the PIC, Research Authorization (where applicable) and Clinical Trial Agreement. The principal investigator should also be available during monitoring visits.

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Committee review, and regulatory inspection (s) by providing direct access to source data/documents. If study site's documents are electronic, these must be made available in their original form (or print outs signed and dated with the statement that this is complete and true reproduction of the original source document) if requested by the sponsor and/or regulatory authority. Study sites should inform Medtronic upon notification of an audit by a regulatory body immediately.

A list of acceptable source documents, are described in section 13, Data Quality and Management.

15.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance, including but not limited to Ethics Committee approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

16 REQUIRED RECORDS AND REPORTS

16.1 Investigator records

The investigator is responsible for the preparation and retention of the records including, but not limited to the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. eCRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the clinical study is terminated. Measures will be taken to avoid loss or premature destruction.

- All correspondence between the Ethics Committee, sponsor, monitor, regulatory authority and/or the investigator that pertains to the clinical study, including required reports.
- Subject's case history records, including:
 - Signed and dated PIC form, in accordance with local requirements
 - Observations of adverse events/adverse device effects/device deficiencies
 - Medical history
 - Baseline, CIED procedure and follow-up data (if applicable)
 - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated eCRFs and blank set of eCRFs where required by local law
- List of investigation sites
- All approved versions of the CIP and PIC
- All approved versions of the Investigator Brochure,
- Signed and dated Clinical Trial Agreement
- Current curriculum vitae of investigators
- Documentation of delegated tasks.
- Ethics Committee approval documentation: written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process. Approval documentation must include the Ethics Committee composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- Study training records for site staff.
- Insurance certificates (EMEA, New Zealand, Latin America, India, ASEAN (Singapore and Malaysia) and Greater China (Hong Kong) only).
- Any other records that local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis.

16.2 Investigator reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the Clinical Investigation Plan. If any action is taken by an Ethics Committee with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Section 9 Adverse Events and Device Deficiencies.

Table 17: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days or local law.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical study.
Final Report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination, or per local requirements.

Table 18: Investigator reports applicable to India

Report	Submit to	Description/Constraints
Agreed termination or suspension	Subjects, Ethics Committee and regulatory authorities	In case the investigator and sponsor agree to prematurely terminate or suspend the study for any reason, the investigator / institution should promptly inform the study subjects, the Ethics Committee as well as the Regulatory Authorities. The investigators should also ensure appropriate therapy and follow-up for the subjects. (<i>India GCP section 3.3.8</i>)
Not agreed termination or suspension	All concerned parties	If the investigator or the sponsor or the Ethics Committee decide to terminate or suspend the study without prior agreement of all parties concerned then the party initiating the suspension / termination should promptly inform all the concerned parties about such suspension / termination and suspension along with a detailed written explanation for such termination / suspension. (<i>India GCP section 3.3.8</i>)

16.3 Sponsor records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- All correspondence which pertains to the clinical study
- Executed CTAs
- Current curriculum vitae of investigators
- Documentation of delegated tasks
- Electronically signed and dated eCRFs
- All approved PIC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates (EMEA, New Zealand, Latin America, ASEAN (Singapore and Malaysia) and Greater China (Hong Kong) only)
- Names/contact addresses of monitors
- Monitoring reports (site qualification visit reports, interim monitoring visit reports and close-out visit reports)
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan, Patient Informed Consent, Investigator's Brochure/ and revisions
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

16.4 Sponsor reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee or regulatory agency, provide accurate, complete and current information about any aspect of the clinical study. Medtronic reporting requirements for safety data are listed in Table 11 of Section 9 (Adverse Events and Device Deficiencies).

Table 19: Sponsor reports for Europe, the Middle East, Africa, Latin America, Greater China (Hong Kong), New Zealand, India, ASEAN (Singapore and Malaysia)

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee, Relevant authorities	Provide prompt notification of termination or suspension and reason(s) per local law,.

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee and relevant authorities	Investigators and other Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, and relevant authorities	Investigators, Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee and regulatory authorities only if required by local law
Final report	Investigators, Ethics Committee, and Regulatory authorities upon request	<ul style="list-style-type: none"> The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal Investigator in each site should be obtained.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. Site-specific study deviations will be submitted to investigators periodically.

Table 20: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, and relevant authorities	Notification within five working days.
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, and relevant authorities	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Final report	Investigators, Ethics Committee, Regulatory authorities upon request	A final report will be submitted to the, investigators, and Ethics Committee s within six months after completion or termination of this study.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. Site specific study deviations will be submitted to investigators periodically.

Report	Submit to	Description/Constraints
Other	IRB,	Accurate, complete, and current information about any aspect of the clinical study.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study. After closure of the study, Medtronic will archive records and reports indefinitely.

APPENDIX A: INFECTION DEFINITIONS

<p>CIED pocket infection</p>	<p>Infection with positive cultures is defined as clinical signs and symptoms of local infection at the generator pocket site (including erythema, warmth, fluctuation, wound dehiscence, erosion, tenderness, or purulent drainage) in addition to microbiological confirmation based on positive cultures on intraoperative samples from purulent discharge, the pocket tissue, explanted CIED, lead tip, or blood. ³⁸</p> <p>Infection with negative cultures is defined as clinical signs and symptoms of local infection at the generator pocket site (including erythema, warmth, fluctuation, wound dehiscence, erosion, tenderness, or purulent drainage) without microbiological confirmation, if the subject received any antibiotic therapy or if there is no other explanation of the localized signs and symptoms. ³⁸</p>
<p>Persistent Bacteremia</p>	<p>Persistent bacteremia is defined as two or more positive blood cultures for typical skin organisms (coagulase-negative staphylococci, <i>Corynebacterium</i> species, <i>Propionobacterium</i> species), or one positive blood culture for all other microorganisms, with or without endocarditis, when no other source is identified to explain the bacteremia and resolution of blood stream infection after device explantation. ³⁸</p> <p>Cases of bacteremia originating from a source other than the CIED that resolve without any evidence of CIED involvement and/or the need for CIED removal should not be considered as CIED infection.</p>

<p>CIED endocarditis</p>	<p>CIED endocarditis is defined as two or more positive blood cultures for typical skin organisms (coagulase-negative staphylococci, <i>Corynebacterium</i> species, <i>Propionibacterium</i> species), or one positive blood culture for all other microorganisms, with positive echocardiographic findings for CIED endocarditis, defined as presence of an oscillating intracardiac mass on cardiac valve or supporting structures, in the absence of an alternative anatomic explanation, or visualization of a cardiac abscess, or new dehiscence of prosthetic valve.^{24,38}</p> <p><u>Vegetation</u> is defined as an oscillating intracardiac mass on the, cardiac valve leaflets, or endocardial surface confirmed by imaging in more than 1 echocardiographic plane, in the absence of an alternative explanation.^{38,43,46,74}</p> <p><u>Intracardiac abscess</u> is defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance by echocardiography or as the presence of pus by direct visualization at the time of surgery.⁴⁶</p> <p>Subcategories of infections:</p> <ul style="list-style-type: none"> • Health care-associated CIED infection • Community acquired CIED infection
<p>Superficial incisional surgical site infection^{75,76}</p>	<p>Superficial incisional surgical site infection (SSI) must meet the following criteria:</p> <p>Infection occurs within 30 days after any National Healthcare Safety Network (NHSN) operative procedure (where day 1 = the procedure date), including other operative procedures not included in the NHSN categories.</p> <p>AND</p> <p>Involves only skin and subcutaneous tissue of the incision.</p> <p>AND</p> <p>Patient has at least one of the following:</p> <ul style="list-style-type: none"> • Purulent drainage from the superficial incision. • Organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision. • Superficial incision that is deliberately opened by a surgeon, attending physician** or other designee and is culture positive or not cultured. <p>AND</p> <p>Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; redness; or heat. A culture negative finding does not meet this criterion.</p> <ul style="list-style-type: none"> • Diagnosis of a superficial incisional SSI by the surgeon or attending physician* or other designee.

<p>Deep incisional surgical site infection 75,76</p>	<p>Deep incisional SSI must meet the following criteria:</p> <p>Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table X.</p> <p>AND</p> <p>Involves deep soft tissues of the incision (e.g., fascial and muscle layers)</p> <p>AND</p> <p>Patient has at least one of the following:</p> <ul style="list-style-type: none"> • Purulent drainage from the deep incision. • A deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician** or other designee and is culture-positive or not cultured. <p>AND</p> <p>Patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture-negative finding does not meet this criterion.</p> <ul style="list-style-type: none"> • An abscess or other evidence of infection involving the deep incision that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test.
<p>Organ/space surgical site infection 75,76</p>	<p>Organ/Space SSI must meet the following criteria:</p> <p>Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table X.</p> <p>AND</p> <p>Infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure.</p> <p>AND</p> <ul style="list-style-type: none"> • Patient has at least one of the following: • Purulent drainage from a drain that is placed into the organ/space • Organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space • An abscess or other evidence of infection involving the organ/space that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test <p>AND</p> <p>Meets at least one criterion for a specific organ/space infection site listed in Table Y.</p>

* Surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).

Table X: Surveillance Period for Deep Incisional or Organ/Space SSI Following Selected NHSN Operative Procedure Categories. Day 1 = the date of the procedure.⁷⁵

30-day surveillance			
Code	Operative Procedure	Code	Operative Procedure
AAA	Abdominal aortic aneurysm repair	LAM	Laminectomy
AMP	Limb amputation	LTP	Liver transplant
APPY	Appendix surgery	NECK	Neck surgery
AVSD	Shunt for dialysis	NEPH	Kidney surgery
BILI	Bile duct, liver or pancreatic surgery	OVRY	Ovarian surgery
CEA	Carotid endarterectomy	PRST	Prostate surgery
CHOL	Gallbladder surgery	REC	Rectal surgery
COLO	Colon surgery	SB	Small bowel surgery
CSEC	Cesarean section	SPLE	Spleen surgery
GAST	Gastric surgery	THOR	Thoracic surgery
HTP	Heart transplant	THYR	Thyroid and/or parathyroid surgery
HYST	Abdominal hysterectomy	VHYS	Vaginal hysterectomy
KTP	Kidney transplant	XLAP	Exploratory Laparotomy
		OTH	Other operative procedures not included in the NHSN categories
90-day surveillance			
Code	Operative Procedure		
BRST	Breast surgery		
CARD	Cardiac surgery		
CBGB	Coronary artery bypass graft with both chest and donor site incisions		
CBGC	Coronary artery bypass graft with chest incision only		
CRAN	Craniotomy		
FUSN	Spinal fusion		
FX	Open reduction of fracture		
HER	Herniorrhaphy		
HPRO	Hip prosthesis		
KPRO	Knee prosthesis		
PACE	Pacemaker surgery		
PVBY	Peripheral vascular bypass surgery		
RFUSN	Refusion of spine		
VSHN	Ventricular shunt		

Note: Superficial incisional SSIs are only followed for a 30-day period for all procedure types.

Table Y: Specific Sites of an Organ/Space SSI.⁷⁵

Code	Site	Code	Site
BONE	Osteomyelitis	LUNG	Other infections of the respiratory tract
BRST	Breast abscess or mastitis	MED	Mediastinitis
CARD	Myocarditis or pericarditis	MEN	Meningitis or ventriculitis
DISC	Disc space	ORAL	Oral cavity (mouth, tongue, or gums)
EAR	Ear, mastoid	OREP	Other infections of the male or female reproductive tract
EMET	Endometritis	OUTI	Other infections of the urinary tract
ENDO	Endocarditis	PJI	Periprosthetic Joint Infection
EYE	Eye, other than conjunctivitis	SA	Spinal abscess without meningitis
GIT	GI tract	SINU	Sinusitis
HEP	Hepatitis	UR	Upper respiratory tract
IAB	Intraabdominal, not specified	VASC	Arterial or venous infection
IC	Intracranial, brain abscess or dura	VCUF	Vaginal cuff
JNT	Joint or bursa		

APPENDIX B: DATA COLLECTION ELEMENTS (ELECTRONIC CASE REPORT FORMS)

Electronic Case Report Forms (eCRFs) for the WRAP-IT study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

APPENDIX C: PRELIMINARY PUBLICATION PLAN

Publications from the WRAP-IT study will be handled according to Cardiac Rhythm Disease Management Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The WRAP-IT Steering Committee members will serve as members of the Publication Committee, in addition to Medtronic representative(s). This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

- 1) manage elements addressed in the publication plan as outlined in this appendix,
- 2) develop the final Publication Plan under separate cover,
- 3) execute the Publication Plan,
- 4) oversee the publication of primary, secondary and ancillary study results,
- 5) review and prioritize publication proposals,
- 6) provide input on publication content, and
- 7) determine authorship.

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Primary, Secondary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “Medtronic WRAP-IT Clinical Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

Transparency

Transparency of study results will be maintained by the following means:

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, Ethics Committees and Competent Authorities of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

APPENDIX D: DATA MONITORING COMMITTEE (DMC)

Point	Examples
DMC will be used	Ongoing oversight for this study will be provided by an independent Data Monitoring Committee (DMC). It is anticipated that the DMC will meet periodically during the study to review the accumulating data.
Who will be involved	<p>The DMC will have one statistician, at least one physician specializing in electrophysiology and at least one specializing in infections. A chairperson from among those members will be identified. None of the DMC members will be participating investigators in the WRAP-IT study.</p> <p>Sponsor clinical staff, except for the sponsor statistician(s) and/or statistical programmer(s) (or designates) preparing the closed DMC report will remain blinded to any aggregate study results separated by treatment group during the course of the study. The DMC charter will outline the procedures for maintaining the confidentiality of unblinded aggregate study data.</p>
Responsibility of the DMC	<p>The DMC will be responsible for assessing the <i>safety and efficacy</i> of the interventions during the study, assessing the scientific soundness with respect to study conduct, accruing data, and external developments, and for monitoring the overall conduct of the clinical study. To enhance the integrity of the study, the DMC may also formulate recommendations related to the selection, recruitment, and retention of subjects, their management, improvement of adherence to protocol-specified regimens and procedures for data management and quality control.</p> <p>The DMC is retained to assess the safety of the interventions during the study on an ongoing basis and evaluate the unblinded study results at the predefined interim analysis. The DMC is also retained to monitor the overall conduct of the study.</p> <p>The DMC will periodically review safety data and the conduct of the trial, review results of the interim analyses, and provide recommendations to the Steering Committee and study sponsor regarding continuation of the study and modifications in design and conduct.</p>

Point	Examples
Recommendations	<p>The DMC will be advisory to the sponsor. The DMC may provide recommendations for early termination of the study or early release of unblinded study results based on the interim analysis. Review and consensus by the entire committee is required to recommend that the study should be stopped or unblinded results disseminated.</p> <p>The DMC may also make recommendations related to the selection, management and retention of subjects, improvement of adherence to protocol-specified regimens, and procedures for data management and quality control.</p> <p>The DMC may monitor the CIED infection rates in the study on an ongoing basis, and if necessary, they may recommend randomizing more subjects in order to ensure enough CIED infections occur to adequately assess the primary study objective. The DMC may also recommend early study termination if an adequate CIED infection rate cannot be achieved in the control group.</p>
Decision Boundaries (if there are pre-determined stopping rules)	<p>Statistical decision boundaries for the study are outlined in the statistical methods section of this document. These are to be used only as guidelines by the DMC when deciding whether the study objectives have been met.</p> <p>The DMC may provide recommendations to unblind and disseminate the study results early based on the interim analysis. In order to recommend early dissemination of the study results, the primary objective must meet the predetermined decision boundary. At the interim analysis, the DMC assessment will balance the evidence on the primary study objective as well as evidence relating to the secondary study objectives. In addition, other considerations for early dissemination of study results may include, but are not limited to, the magnitude of effect, secondary objectives, data quality, and consistency of results across subgroups. In the event that a decision is made to unblind the study following the interim analysis, the DMC may recommend that the study continue to enroll and follow subjects to evaluate the effect of the TYRX envelope on CIED infections that develop post-12-months as well as collect additional follow-up in subjects with a defibrillation system in which to evaluate the lead monitoring features. However, the DMC may recommend that subjects no longer be randomized in the TYRX envelope is found to have a clear benefit.</p>

APPENDIX E: STUDY OVERVIEW

Title

World-wide Randomized Antibiotic Envelope Infection Prevention Trial.

Short title

WRAP-IT

Purpose

Medtronic, Inc. is sponsoring the World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT), a randomized, prospective, multi-center, single blinded, post-market, interventional clinical study. The study has three purposes. First, the WRAP-IT study will serve as a post-approval study for those geographies requiring a post-approval study to facilitate collection of complications related to the Cardiovascular Implantable Electronic Device (CIED) procedure or system in subjects randomized to receive the TYRX™ Absorbable Antibacterial Envelope (henceforth referred to as TYRX envelope). Next, this study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, revision, or *de novo* CRT-D implant. Subjects undergoing CIED generator replacement, upgrade, revision or the implant of a *de novo* CRT-D system will be randomized to either receive the TYRX envelope or not to receive the TYRX envelope. Randomization will be 1:1 and be stratified by study site and device type high power (ICD and CRT-D) vs. low power devices (IPG and CRT-P). Finally this large device study provides the unique opportunity to prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead. These features include the lead integrity alert (LIA), lead noise alert (LNA), RV pacing impedance, and high voltage (HV) pacing impedance to detect events that affect a RV lead's pacing, sensing, or defibrillation circuit lead system events (LSE).

Design

The study is expected to be conducted at up to 225 sites worldwide with up to 7,764 subjects enrolled in order to randomize approximately 6,988 subjects. Enrollment of subjects receiving a replacement low power device (i.e. IPG or CRT-P) will be capped at approximately 25% of the total randomized study population (i.e. approximately 1,746 subjects). Relative to high power device recipients, patients receiving a low power device may be at reduced risk of a major CIED infection. Thus, to ensure an adequate CIED infection event rate in the control arm, there is a desire to include a higher proportion of high power devices in the trial.

The enrollment period is expected to start in late 2014 and to take approximately 24 months. Subjects will be followed for a minimum of 12 months. The anticipated study duration is approximately 36 months and subjects may be followed for up to 36 months depending on when they enroll in the study.

Expected participating geographies include, but are not limited to, the United States (US), Europe, the Middle East and Africa (EMEA), Greater China (Hong Kong), New Zealand, Latin America, the Association of South East Asian Nations (ASEAN) (Singapore and Malaysia), and India.

To ensure a widespread distribution of data, minimize site bias in study results and ensure that sites will be able to adequately manage and follow subjects enrolled in the study, the maximum number of randomized subjects allowed at a single site is 100 subjects. Sites are encouraged to enroll as many consecutive eligible subjects as appropriate. There is no specific minimum number of enrollments required, except where stated in the clinical trial agreement between the sponsor and the individual site.

Medical device

The Medtronic TYRX envelope is an absorbable sterile prosthesis designed to hold a pacemaker pulse generator or defibrillator to create a stable environment when implanted in the body. The TYRX envelope is constructed from multifilament knitted mesh (polymer made of glycolide, caprolactone, and trimethylene carbonate) that is coated with an absorbable polyarylate polymer. The purpose of the absorbable coating is to act as a carrier for the antimicrobial agents. The absorbable antibacterial envelope absorbable polymer coating contains antimicrobial agents in concentrations of 8.0 mg rifampin and 5.1 mg minocycline (Medium size, IPG), and 11.9 mg rifampin and 7.6 mg minocycline (Large size, ICD). The TYRX envelope releases the antimicrobial agents rifampin and minocycline for a minimum of 7 days to reduce the risk of infection of the implanted CIED following surgery. The TYRX envelope will be used in combination with market-released Medtronic CIED generator replacement, upgrade, revision or implant of a *de novo* CRT-D system with any commercially released RV, RA (if applicable), and LV (if applicable) leads.

Objectives and endpoints

Primary objective

The primary study objective is to compare the rate of major CIED infections through 12-months post-procedure between the TYRX envelope group and the control group (no TYRX envelope).

Secondary objectives

- Confirm that the TYRX envelope does not increase the CIED procedure-related or system-related complication rate through 12-months post-procedure.
- Compare the major CIED infection rate during the entire follow-up between the TYRX envelope group and the control group.
- Compare the rate of major and minor CIED infections through 12-months post-procedure between the TYRX envelope group and the control group.

Ancillary objectives

- Compare all-cause mortality rates between the TYRX envelope group and the control group
- Evaluate the CIED procedure success rate in the TYRX envelope group and the control group
 - Control: device and leads all implanted
 - Treatment: TYRX envelope, device, and leads all implanted

- Summarize the adverse events
- Identify the predictors of CIED infection
- Summarize quality of life
- Evaluate the cost effectiveness of the TYRX envelope



Primary endpoint

Major CIED infections are defined as CIED infections resulting in one or more of the following:

- CIED system removal
- Any invasive procedure (e.g. pocket opened) without system removal
- Treatment with antibiotic therapy if the subject is not a candidate for system removal and infection recurrence after completion of antibiotic therapy or evidence of deep infection with wound dehiscence, erosion, or purulent drainage.
- Death

Note: All other CIED infections including superficial incisional SSIs that meet the CDC criteria, independent of the time from surgery, are defined as minor CIED infections unless they meet the major CIED infection criteria.

Subject population

Subjects meeting one or more of the following criteria may be enrolled: 1) an ACC/AHA/HRS or ESC guideline-recommended need for a *de novo* CRT-D and subject has a geography approved indication for a CRT-D, 2) an existing IPG, CRT-P, ICD, or CRT-D undergoing generator replacement or generator upgrade with or without the addition of new leads, or 3) an existing IPG, CRT-P, ICD, or CRT-D undergoing a CIED system revision procedure (6,988 randomized subjects (3,494 randomized to each group)). Subjects who enroll in the study and proceed with a device procedure must be implanted with a Medtronic single, dual, or triple chamber pacemaker or defibrillator that has received appropriate license or regulatory approval and is commercially available by Medtronic in the geography in which the procedure will take place. Any market-released, commercially available transvenous lead(s) can be used in this study. The

total study duration is expected to be approximately 36 months, including 24 months for subject recruitment and 12 months for subject follow-up.

Treatment

Subjects undergoing CIED generator replacement, upgrade, or revision or the implant of a *de novo* CRT-D system with a new Medtronic CIED will be randomized to either receive the TYRX envelope or not to receive the TYRX envelope. Randomization will be 1:1 and be stratified by study site and device type (high power (ICD and CRT-D) vs. low power devices (IPG and CRT-P)).

Due to the nature of the CIED procedure, it is not possible to blind the implanting investigator or study site staff. However, efforts should be employed to blind the study subject to their randomized treatment throughout the duration of the study. In particular, efforts to keep the subject blinded to their randomized treatment in the procedure room will be necessary in the setting of conscious sedation. All randomized subjects will be unblinded at the end of the study.

Inclusion criteria

Patients must meet the following inclusion criteria to be eligible to participate in the study:

- Patient is willing to sign and date the study Patient Informed Consent (PIC) Form
 - Patient is at least 18 years of age and meets age requirements per local law
 - Patient is planned to undergo at least one of the following:
 - a. Patient has existing CIED and is undergoing IPG (including CRT-P), ICD or CRT-D replacement or upgrade with a new Medtronic generator
 - i. Subjects planned to have leads added, or extracted and added for upgrades can be enrolled
- OR
- b. Patient will undergo a *de novo* Medtronic CRT-D system implant per approved indications
- OR
- c. Patient has existing study eligible Medtronic CIED in which the pocket was not accessed within the last 365 days, and is undergoing pocket or lead revision
- Willing to provide the contact information for the physician who provides follow-up for his/her CIED.
 - Willing and able to comply with scheduled follow-up and study related activities.

Exclusion criteria

Patients must not meet any of the following exclusion criteria to be eligible to participate in the study:

- Known allergy to minocycline or rifampin or their derivatives, or any other known contraindications to implantation of the TYRX envelope.
- Current therapy with chronic oral immunosuppressive agents or $\geq 20\text{mg/day}$ of Prednisone or equivalent.
- Hemodialysis or peritoneal dialysis.

- Prior Cardiac transplantation or existing Ventricular Assist Device (VAD).
- Require long-term vascular access for any reason.
- Prior history of a CIED infection, other prosthetic device infection, or endovascular infection, including endocarditis, in the past 12 months.
- Physical, clinical, or laboratory signs or symptoms consistent with an active infection (including but not limited to pneumonia, urinary tract, cellulitis, or bacteremia)
- Systemic lupus erythematosus, because minocycline has been reported to aggravate this condition
- Female patient who is pregnant, or of childbearing potential and not on a reliable form of birth control. Women of childbearing potential are required to have a negative pregnancy test within 7 days prior to device procedure
- Participation in another study that may confound the results of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager.

Clinical Procedures

Study Procedure	Baseline	Procedure	Pre-Hospital Discharge	Biannual Follow-up Visits	Unscheduled Visit	Study Exit
Patient Informed Consent	X					
Inclusion/Exclusion Assessment	X					
Subject Demographics	X					
Record Medications ¹	X	X	X	X	X	X
Medical History	X					
System and Procedure Information		X				
Confirm Programming Requirements (subjects with ICD or CRT-D only)		X	X	X		
Evaluate Subject for Signs and Symptoms of CIED Infection			X	X	X	X
Evaluate Subject and Device for LSEs			X	X	X	X
Final Device Interrogation / CareLink [®] Transmission		X	X	X	X	X

Study Procedure	Baseline	Procedure	Pre-Hospital Discharge	Biannual Follow-up Visits	Unscheduled Visit	Study Exit
EQ-5D	X			X (12 month visit only)		X (Only if exited prior to 12 month visit)
Collect or Confirm Contact Information of CIED follow-up Physician ²	X		X	X		
Exit Subject						X
CIED Infection	As they occur					
CIED Infection-Related Health Care Utilization	As they occur					
CIED Infection-Related EQ-5D	Within 2 weeks following a diagnosis of CIED infection, and subsequently 1, 3, and 6 months post infection diagnosis					
Lead System Event (ICD and CRT-D Subjects only)	As they occur					
Holter for Suspected LSE if required (ICD and CRT-D Subjects only)	As they occur					
Adverse Events (AEs)	As they occur					
Device Deficiencies	As they occur					
System Modifications	As they occur					
Study Deviations	As they occur					
Device Disposition for TYRX envelope	As it occurs in geographies where required					
Death	As it occurs					

¹ Record any anti-platelet agents, anticoagulants, antibiotics, corticosteroids, insulin or oral diabetic agents.

² The CIED follow-up physician could also be the referring cardiologist or other physician overseeing care of the patient following procedure.

Subjects are considered enrolled in the study upon signing the PIC. Enrolled subjects are eligible for randomization after completion of the baseline assessment and if all inclusion and none of the exclusion criteria are met. Randomized subjects may be followed for up to 36 months depending on when they enroll in the study. After Baseline and Procedure, subjects will return for biannual follow-ups up until their study exit.

Study Follow-up Visit	Window (Calculated days post-CIED procedure)		
	Window Start (days post-procedure) ¹	Target (days post-procedure)	Window End (days post-procedure)
6-Month	168	183	198
12-Month	365	365 ²	395
18-Month	521	549	577
24-Month	702	730	758
30-Month	887	915	943
36-Month	1070	1098	1126

¹Days post-randomization if subject never had a CIED procedure attempt.

²The target date and window start date intended to be equal for primary objective analysis purposes.

APPENDIX F: PATIENT INFORMED CONSENT TEMPLATES

Geography-specific Patient Informed Consent (PIC) templates will be provided under separate cover.

APPENDIX G: FORESEEABLE ADVERSE EVENT LIST

The information provided in this section pertains to foreseeable adverse events that may be observed in WRAP-IT subjects and may assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse events information may be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The implantation of the CIED system and the TYRX™ Absorbable Antibacterial Envelope (henceforth referred to as TYRX envelope) involves surgery. Therefore, standard adverse events associated with a surgical procedure may be experienced, such as anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc. However, the focus of this section is to specifically address those events that are foreseeable due to the implantation, use, performance, and/or presence of the system under investigation.

Potential risks associated with the implantation of the CIED system and the TYRX envelope as well as risk minimization are discussed within section 10. Treatment required for procedure- and/or system-related adverse events that are experienced may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies.

The list of foreseeable TYRX envelope-related adverse events and adverse device effects is composed based on the Instructions For Use, Label submitted to the notified body, the Combined 6 Month Analysis of Centurion and Citadel Clinical Studies and the Clinical Evaluation Report for the TYRX™ Non-Absorbable Antibacterial Envelope and TYRX™ Absorbable Antibacterial Envelope. The foreseeable TYRX envelope-related adverse events include, but are not limited to, the following:

Foreseeable TYRX envelope-related Adverse Events and Adverse Device Effects

Generator or lead malfunction	Adhesions	Minocycline allergic reaction
Generator dislodgement or migration	Hematoma	Minocycline side effects
Lead dislodgement or migration	Inflammation	Allergic reaction to resorbable suture-like components
Lead fracture	Extrusion	TYRX envelope may complicate generator removal and replacement
Skin erosion	Fistula formation	Additional stress on the hepatic and renal systems
Wound dehiscence	Unresolved infection that may require removal of prosthesis	
Bleeding	Rifampin allergic reaction	
Infection	Rifampin side effects	
Seroma		

The adverse events associated with the use of transvenous leads, pacing and defibrillation systems include, but are not limited to, the following:

Foreseeable CIED-related Adverse Events and Adverse Device Effects

Acceleration of tachyarrhythmias	Hemothorax	Pocket erosion
Air embolism	Impedance increased	Pulmonary/pleural effusion
Angina pectoris	Implant delivery tool problem	Sepsis
Anxiety	Implant site bruising	Septic shock
Atrial arrhythmia	Implant site cellulitis	Subcutaneous emphysema
Bleeding/hemorrhage	Implant site discharge	Syncope
Cardiac (heart wall or vein wall) rupture	Implant site erythema	Thromboembolism
Cardiac dissection	Implant site fibrosis	Thrombosis
Cardiac perforation	Implant site hematoma	Tissue necrosis
Cardiac tamponade	Implant site infection	Transient ischemic attack
Cardiac vein dissection	Implant site necrosis	Twiddler's syndrome
Cardiac vein perforation	Implant site pain	Undersensing
Cerebrovascular accident	Implant site seroma	Valve damage
Coronary sinus dissection	Implant site swelling	Vasovagal reaction
Coronary sinus perforation	Inappropriate device signal detection	Venous occlusion
Deep vein thrombosis	Inappropriate device therapy	Venous stenosis
Depression	Inappropriate extra-cardiac device stimulation	Ventricular arrhythmia
Device battery issue	Incision site hematoma	
Device connection issue	Infection	
Device electrical impedance issue	Keloid scar	
Device lead damage	Lead abrasion and discontinuity	
Device lead fracture	Lead conductor failure	
Device migration	Lead connector failure	
Device protrusion/extrusion	Lead dislodgement	
Device rejection	Lead insulation failure	
Dysplasia	Loss of capture	
Electrical conduction disorders	Myocardial damage	
Electromagnetic interference	Myocardial infarction	
Elevated pacing threshold	Myocardial irritability	
Emotional distress	Myopotential sensing	
Endocarditis	Nerve damage	
Erosion	Oversensing	
Exit block	Pacemaker syndrome	
Failure to capture	Pericardial effusion	
Far-field R-wave sensing	Pericardial hemorrhage	
Fibrotic tissue growth	Pericardial rub	
Fluid accumulation	Pericarditis	
Heart block	Phrenic nerve stimulation	
Heart failure worsening	Pneumothorax	

APPENDIX H: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

At the time of WRAP-IT Clinical Investigation Plan (CIP) Version 1.0 completion, site confirmation was not finalized. A complete list of participating investigators and institutions (including names, titles, address(es), and telephone numbers) where study activities will be conducted will be distributed under a separate cover when available. Approval of the WRAP-IT CIP will be documented by signing the Clinical Trial Agreement or the CIP signature page.

APPENDIX I: ETHICS COMMITTEE

At the time of WRAP-IT Clinical Investigation Plan Version 1.0 completion, site confirmation was not finalized. Therefore, a complete list of participating Ethics Committee and the Chairperson(s) will be distributed under a separate cover when available upon request.

APPENDIX J: LABELING

Labeling and package for all products used in this study will follow the local regulatory requirements. Labeling for all system components market released at study start in the respective geographies (including labeling for the TYRX™ Absorbable Antibacterial Envelope) can be found with each package insert and/or will be available on <http://manuals.medtronic.com>.

APPENDIX K: BIBLIOGRAPHY

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APPENDIX L: PRECLINICAL TESTING

A summary and results of preclinical testing with the TYRX™ Absorbable Antibacterial Envelope is provided in the Investigator's Brochure.

APPENDIX M: PREVIOUS CLINICAL STUDIES

A summary of and results from previous clinical studies related to the WRAP-IT study or devices with similar features is provided in the Investigator's Brochure.

APPENDIX N: COMMITTEES

Steering Committee

A Steering Committee (SC) will serve to oversee and guide the conduct of the study as well as develop publications and presentations. The SC is independent from Medtronic, Inc. and will be blinded to the study data while the study is ongoing.

The Steering Committee will serve as a publication committee and will be primarily responsible for the creation, review, and submission of publications and presentations related to the study. A publication plan will be developed in conjunction with the Sponsor prior to the start of the trial. This publication plan may need to be adjusted, as appropriate, based on the progress of the study.

Data Monitoring Committee

A Data Monitoring Committee (DMC) will be independent of Medtronic, Inc. and the Executive Steering Committee. The committee will not include any investigators involved with the study. The Executive Steering Committee Chair and Medtronic, Inc. will collaborate to appoint the DMC. The DMC will evaluate the safety results as well as conduct an interim analysis during the course of the study. The membership and responsibilities of the DMC will be defined in a separate document entitled the *Data Monitoring Committee Charter*.

Clinical Event Committee

A Clinical Events Committee (CEC) will provide an independent and blinded assessment of the study endpoints as defined in the CEC Charter, based on standardized classifications and definitions. The members of this committee will not directly participate in the conduct of the study and will be blinded to treatment allocation throughout the conduct of the study.

APPENDIX O: CLINICAL INVESTIGATION PLAN SIGNATURE PAGE (ONLY APPLICABLE IF NOT COVERED IN THE CTA)

WRAP-IT

The WRAP-IT is a randomized, prospective, multi-center, single blinded, post-market, interventional clinical study. The study has three purposes. First, the WRAP-IT study will serve as a post-approval study for those geographies requiring a post-approval study to facilitate collection of complications related to the Cardiovascular Implantable Electronic Device (CIED) procedure or system in subjects randomized to receive the TYRX™ Absorbable Antibacterial Envelope (henceforth referred to as TYRX envelope). Next, this study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, revision, or *de novo* CRT-D implant. Finally this large device study provides the unique opportunity to prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead.

Clinical Investigation Plan Version 1.0 – 29 JUL 2014

I/we acknowledge that I/we have read, understood and agreed to abide by all conditions, instructions and restrictions contained in the above mentioned Clinical Investigation Plan. I/we agree to carry out all of its items in accordance with applicable regulations and in full compliance with the guidelines.

Hospital		
Title, First and last Name	Signature	Date (dd/MMM/yyyy)

APPENDIX P: MODEL NUMBERS OF THE MARKET-RELEASED IPGs, CRT-Ps, ICDs AND CRT-Ds IN THE RESPECTIVE GEOGRAPHIES

Device	Model	Respective Geography Model Numbers											
		United States	ANZ	Latin America	Brazil	Western Europe	CEE	Middle East	South Africa	Hong Kong	India	Malaysia	Singapore
IPG	Adapta	ADDR03 ADDR06 ADDRL1 ADDRS1 ADDRS1P ADSR01P ADSR03 ADSR06 ADDR01 ADSR01 ADVDD01	ADDR03 ADDR06 ADDRL1 ADDRS1 ADDRS1 ADSR01P ADSR03 ADSR06 ADDR01 ADSR01 ADVDD01	ADDR03 ADDRL1 ADDRS1 ADDRS1P ADSR06 ADSR06 ADDR01 ADSR01 ADVDD01	ADDR03 ADDR06 ADDRS1 ADSR03 ADSR06 ADDR01 ADSR01	ADDR01P ADDR03 ADDR06 ADDRL1 ADDRS1 ADSR03 ADSR06 ADD01 ADSR01 ADSR06 ADD01 ADDR01 ADSR01 ADVDD01	ADDRL1 ADDRS1 ADSR06 ADDR01 ADSR01	ADDR03 ADDRL1 ADSR03 ADD01 ADSR01 ADVDD01	ADDR03 ADDRL1 ADSR03 ADSR06 ADDR01 ADVDD01	ADDR03 ADDRL1 ADDRS1 ADSR03 ADSR06 ADDR01 ADSR01	ADDRL1 ADD01 ADDR01 ADSR01 ADVDD01	ADDRL1 ADDR01 ADSR03 ADSR01 ADVDD01	ADDR03 ADDRL1 ADSR06 ADDR01 ADSR01 ADVDD01
	Advisa	A2DR01 A4DR01	A3DR01 A5DR01	A2DR01 A3SR01	A3DR01 A5DR01	A3DR01 A3SR01 A5DR01	A3DR01	A3DR01 A5DR01	A3DR01	A3DR01 A5DR01	A3DR01	A3DR01 A5DR01	A3DR01 A5DR01
	Ensura		EN1DR01	EN1DR01	EN1DR01	EN1DR01 EN1SR01	EN1DR01	EN1DR01	EN1DR01	EN1DR01	EN1DR01	EN1DR01	EN1DR01
	Relia		REDR01 RESR01	EDR01 RES01 RESR01 REVDD01		RED01 REDR01 RES01 RESR01 REVDD01	RED01 REDR01 RES01 RESR01 REVDD01	REDR01 RES01 RESR01 REVDD01	REDR01 RESR01	RED01 REDR01 RES01 RESR01 REVDD01	RED01 REDR01 RES01 RESR01 REVDD01	RED01 REDR01 RES01 RESR01 REVDD01	RED01 REDR01 RES01 RESR01 REVDD01
	Revo	RVDR01		RVDR01									

	Sensia	SEDR01 SESR01	SEDRL1 SEDR01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01	SEDR01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01	SEDRL1 SED01 SEDR01, SES01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01	SED01 SEDR01 SES01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01	SEDRL1 SED01 SEDR01 SES01 SESR01
	Versa	VEDR01	VEDR01	VEDR01		VEDR01	VEDR01		VEDR01				
CRT-D	Brava					DTBC2D1 DTBC2D4	DTBC2D1 DTBC2D4	DTBC2D1 DTBC2D4	DTBC2D1		DTBC2D4		DTBC2D1 DTBC2D4
	Brava Quad					DTBC2Q1 DTBC2QQ	DTBC2QQ	DTBC2Q1 DTBC2QQ			DTBC2QQ		DTBC2Q1 DTBC2QQ
	Protecta	D334TRG D334TRM	D364TRG D364TRM	D364TRG		D364TRG D364TRM	D364TRG D364TRM	D364TRG D364TRM	D364TRM	D364TRM	D364TRG D364TRM	D364TRG	D364TRM
	Protecta XT	D314TRG D314TRM	D354TRG D354TRM	D314TRG D314TRM D354TRG D354TRM	D314TRG D354TRG D354TRM	D354TRG D354TRM	D354TRG D354TRM	D354TRG D354TRM	D354TRG D354TRM	D354TRG D354TRM	D354TRG D354TRM	D354TRM	D354TRG D354TRM
	Viva S	DTBB1D1 DTBB1D4	DTBB2D1 DTBB2D4			DTBB2D1 DTBB2D4		DTBB2D1 DTBB2D4		DTBB2D1 DTBB2D4		DTBB2D4	DTBB2D4
	Viva S Quad		DTBB2QQ			DTBB2QQ		DTBB2QQ		DTBB2QQ			
	Viva XT	DTBA1D1 DTBA2D1	DTBA2D1 DTBA2D4			DTBA1D1 DTBA2D1 DTBA2D4	DTBA2D1 DTBA2D4	DTBA2D1 DTBA2D4	DTBA2D1 DTBA2D4	DTBA2D1 DTBA2D4	DTBA2D1 DTBA2D4	DTBA2D1 DTBA2D4	
	Viva XT Quad		DTBA2Q1 DTBA2QQ	DTBA2QQ		DTBA2Q1 DTBA2QQ	DTBA2Q1 DTBA2QQ	DTBA2Q1 DTBA2QQ	DTBA2QQ	DTBA2QQ	DTBA2QQ	DTBA2QQ	DTBA2QQ
CRT-P	Consulta	C4TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01	C3TR01
	Syncra	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01	C2TR01
	Viva XT	C5TR01	C5TR01			C5TR01							

ICD	Evera S	DDBC3D1 DDBC3D4 DVBC3D1 DVBC3D4	DDBC3D1 DDBC3D4 DDMC3D4 DVBC3D1 DVBC3D4 DVBC3D4 DVMC3D4			DDBC3D1 DDBC3D4 DDMC3D4 DVBC3D1 DVBC3D4 DVMC3D4	DVBC3D1	DDBC3D1 DDBC3D4 DDMC3D4 DVBC3D1 DVBC3D4 DVMC3D4				DDBC3D1 DDBC3D4 DDMC3D4 DVBC3D1 DVBC3D4	DDBC3D1 DDBC3D4 DVBC3D4
	Evera XT	DTBB1D1 DTBB1D4 DVBB1D1 DVBB1D4	DDBB2D1 DDMB2D4 DTBB2D4 DVBB2D1 DVBB2D4 DVMB2D4	DDBB2D1 DTBB1D4		DDBB2D1 DDMB2D4 DTBB2D4 DVBB2D1 DVBB2D4 DVMB2D4	DDBB2D1 DTBB2D4 DVBB2D1 DVBB2D4 DVMB2D4	DDBB2D1 DDMB2D4 DTBB2D4 DTBB2D4 DVBB2D1 DVBB2D4 DVMB2D4	DDBB2D1 DDMB2D4 DTBB2D4 DTBB2D4 DVBB2D1 DVBB2D4 DVMB2D4	DDBB2D1 DDMB2D4 DTBB2D4 DTBB2D4 DVBB2D1 DVBB2D4 DVMB2D4		DDBB2D1 DDMB2D4 DTBB2D4 DVBB2D1 DVBB2D4	DDBB2D1 DTBB2D4 DVBB2D4
	Protecta	D334DRG D334DRM D334VRG D334VRM	D364DRG D364DRM D364VRG D364VRM	D364VRG		D364DRG D364DRM D364VRG D364VRM	D364DRG D364DRM D364VRG D364VRM	D364DRG D364DRM D364VRG D364VRM		D364DRG D364DRM	D364DRG D364DRM D364VRG D364VRM	D364DRM D364VRG D364VRM	D364DRM D364VRG D364VRM
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Alleviating Pain · Restoring Health · Extending Life

**World-wide Randomized
Antibiotic Envelope
Infection Prevention Trial
(WRAP-IT)**

Statistical Analysis Plan

Version 1.0
July 21, 2015

Pei Li, Sr Statistician
Kurt Stromberg, Sr Principal Statistician

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3.5	[REDACTED]
	[REDACTED]
	[REDACTED]
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[REDACTED]	[REDACTED]
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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

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1 PURPOSE

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design of the WRAP=IT study, and the planned analyses that will be included in study reports. This SAP does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected.

2 RATIONALE FOR STUDY DESIGN

The World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP=IT) is a randomized, prospective, multi-center, single blinded, post-market, interventional clinical study. The study has three purposes. First, the WRAP=IT study will serve as a post-approval study for those geographies requiring a post-approval study to facilitate collection of complications related to the Cardiovascular Implantable Electronic Device (CIED) procedure or system in subjects randomized to receive the TYRX™ Absorbable Antibacterial Envelope (henceforth referred to as TYRX envelope). Next, this study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, or revision, or the implant of a de novo CRT=D. Subjects undergoing CIED generator replacement, upgrade, or revision or the implant of a de novo CRT=D system will be randomized to either receive the TYRX envelope or not to receive the TYRX envelope. Randomization will be 1:1 and be stratified by study site and device type, high power (ICD and CRT=D) vs. low power devices (IPG and CRT=P). Finally this large device study provides the unique opportunity to prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead. These features include the lead integrity alert (LIA), lead noise alert (LNA), RV pacing impedance, and high voltage (HV) pacing impedance to detect events that affect a RV lead's pacing, sensing, or defibrillation circuit lead system events (LSE).

The study is expected to be conducted at up to 225 sites worldwide with up to 7,764 subjects enrolled in order to randomize approximately 6,988 subjects. Enrollment of subjects receiving a replacement low power device (i.e. IPG or CRT=P) will be capped at approximately 25% of the total randomized study population (i.e. approximately 1,746 subjects). Relative to high power device recipients, patients receiving a low power device may be at reduced risk of a major CIED infection. Thus, to ensure an adequate CIED infection event rate in the control arm, there is a desire to include a higher proportion of high power devices in the trial.

The WRAP=IT study utilizes a group sequential design and has up to two planned analyses of the primary objective. The first analysis will occur when a minimum of 3,200 randomized subjects complete the 6-month visit and the final analysis will occur when all randomized subjects have the opportunity to complete the 12-month study visit. The study may be considered successful at the first analysis in which the primary objective is met. An independent Data Monitoring Committee (DMC) will periodically review the accumulating data and review the results of the analysis of the primary objective at each pre-specified analysis time point. Should the DMC indicate that the study is successful at the interim analysis, the study may continue to enroll and follow subjects to evaluate the effect of the TYRX envelope on CIED infections that develop post=12 months as well as collect additional follow-up in subjects with a defibrillation system in which to evaluate the lead monitoring features. However, subjects enrolled following review of the interim analysis may no longer be randomized upon recommendation of the DMC if the TYRX envelope is found to have a clear benefit.

The WRAP=IT Study Clinical Investigational Plan Version 1.0 was used to develop the SAP.

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Description of Baseline Variables

Standard baseline and relevant medical history will be collected on the eCRFs for all enrolled subjects. Baseline and medical history variables to be summarized include, but are not limited to: age, sex, race, device type (CRT-D, ICD, CRT-P, and IPG), number of previous CIED devices, NYHA class, arrhythmia history, and baseline medication use.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Baseline information will be summarized for all randomized subjects. The TYRX envelope and control groups will be compared using T-tests for continuous variables and the Chi-square test for categorical variables to quantify any imbalance in treatment groups.

3.1.2 Special Considerations

3.1.2.1 Pooling

The study may be conducted at up to 225 sites worldwide. Data from all centers that participate in this protocol will be combined for analysis. Expected participating geographies include, but are not limited to, the United States (US), Europe, the Middle East and Africa (EMEA), Greater China (Hong Kong), New Zealand, Latin America, the Association of South East Asian Nations (ASEAN) (Singapore and Malaysia), and India. However, since the majority of study centers will come from the US and the primary endpoint is likely to be rare, the primary objective results for US and outside the US (OUS) geographies will be presented and poolability analysis will be done. If a differential treatment effect ($P < 0.05$) is observed, we will investigate the cause of the differential treatment effect (e.g. by comparing baseline characteristics, procedure information and the medical practice etc).

3.1.2.2 Missing Data

If applicable, treatment of missing data is addressed within each objective.

3.1.2.3 Visit Windows

As the visit windows are meant as a guideline for centers, data from CRFs dated outside of the prescribed visit windows in the CIP will be used in all analyses.

3.1.2.4 Database Freeze

The visit cut-off date for the database freeze for the interim analysis will be the first date when a minimum of 3200 randomized subjects complete the 6-month visit. The visit cut-off date for the database freeze for the final analysis will be the date when all randomized subjects have had the opportunity to complete the 12-month study visit.

3.1.2.5 Randomization Date

There may be instances where the date and timestamp for the randomization process in the electronic database where randomization is performed may be after the date of the CIED procedure. This occurs when randomization is performed outside of the database (e.g. cases where Oracle Clinical is not accessible by the site) and the randomization

routine in the electronic database is executed to document the randomization process on a later date. For such cases, the randomization date will come from the randomization or implant procedure eCRF, whichever came first.

3.1.2.6 Interim Analysis Type I Error Control

The study has up to two planned analyses of the primary objective. The study may be considered successful at the first analysis in which the primary objective is met.

The first analysis will occur when approximately 50% of the total follow-up within 12-months of randomization occurs; based on enrollment projections described below this is defined as the point where 3200 randomized subjects complete the 6-month post-procedure visit. The purpose of this first analysis is two-fold:

1. To assess whether the study's primary objective has been met. If the DMC indicates that the study has met its objective, the study may continue to enroll and follow subjects to study the effect of the TYRX envelope on long-term CIED infections as well as accumulate LSEs. However, subjects enrolling following review of the interim analysis may no longer be randomized upon recommendation of the DMC if the TYRX envelope is found to have a clear benefit.
2. To assess whether the study may end earlier than planned for futility.

The timing of the interim analysis was selected so that sufficient data is collected to contribute to the interim analysis before decisions that impact the study are made. The Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) is used to control the overall alpha level at 5% (two-sided; 2.5% one-sided in the direction favorable to the TYRX envelope). This function spends the alpha at a level analogous to the O'Brien-Fleming boundary. The boundary condition at the interim analysis will be based on the information fraction at the interim analysis and computed by dividing the accrued number of major CIED infections observed at the interim analysis by the total number of major CIED infections anticipated at the final analysis.

To obtain the information fraction, a simulation will be performed to estimate the anticipated number of events pooled across both treatment groups which are expected to happen after the interim analysis. The event-free survival function is assumed to be piecewise exponential with two intervals (interval cutoff to be determined at interim analysis based on observed data). The hazard parameter in each interval will be estimated by data observed at interim analysis. Then complete follow-up data will be simulated to estimate of number of events by end of study. Sample R code for performing this simulation is found in section 4.2.

Assuming the information fraction at the interim analysis is 50%, the boundary condition at the interim analysis is 0.003 (2.75 on the Z-scale or 0.006 on the two-sided p-value scale) and is purposely low to allow early claims of study success only when the TYRX envelope is highly effective. At the final analysis, the boundary condition is 0.0238 (1.98 on the Z-scale or 0.0476 on the two-sided p-value scale) when the information fraction is 50% at the interim analysis. Since the analytical methods for the secondary objectives also utilize survival analysis methods, the same alpha spending function will be used to compute the success boundaries for the secondary objectives.

If the primary objective of the study is met, the secondary objectives will be tested using the Holm procedure to protect the overall type I error rate of the study and allow statistically valid claims of significance. Specifically, at analysis k ($k=1,2$), the ordered hypotheses $H_{(1k)}, H_{(2k)}, H_{(3k)}$ corresponding to the ordered p-values $p_{(1k)}, p_{(2k)}, p_{(3k)}$ of the secondary objectives will be tested based off the sequentially rejective algorithm. The hypothesis $H_{(1k)}$ is rejected if $p_{(1k)} \leq$

$\alpha_k/3$. Further, $H_{(jk)}$ is rejected at the j^{th} step if $p_{(jk)} \leq \alpha_k/(3 - j + 1)$. Otherwise, $H_{(jk)}$, $H_{(3k)}$ are retained and the algorithm terminates.

To help assess whether the study may end earlier than planned for futility, stochastic curtailment methods will be used to calculate the futility index for the primary objective. The futility index ($1 - P_1$, where P_1 is the predictive power observed at the interim analysis) is based on predictive power as computed as:

$$P_1 = \Phi \left\{ \frac{Z_1 \sqrt{I_2} - z_\alpha \sqrt{I_1}}{\sqrt{I_2 - I_1}} \right\}$$

where Z_1 is the test statistic at the interim analysis, I_1 is the information fraction at the interim analysis, I_2 is the information fraction at the final analysis (will be considered 1 at the interim analysis), and z_α is the critical value at the final analysis based on the alpha spending function. Although non-binding, a futility index greater than 0.9 at the interim analysis provides strong evidence that the study will not achieve its primary objective if the study were to continue to its full sample size and follow-up.

3.1.3 Early Study Success

Should the DMC indicate that the study is successful at the interim analysis, the study may continue to enroll and follow subjects to evaluate the effect of the TYRX envelope on CIED infections that develop post 12 months as well as collect additional follow-up in subjects with a defibrillation system in which to evaluate the lead monitoring features. If the study were to continue to enroll, it is anticipated that all subjects enrolled after the interim analysis would receive the TYRX envelope. Thus, for the final report, only those subjects randomized prior to the decision to end randomized allocation of the TYRX envelope would be included in the analysis of the primary and secondary objectives as well as ancillary objective #1.

3.1.4 Reports for which this Statistical Analysis Plan applies

This SAP applies to the interim analysis report and final report. However, the interim analysis report will likely evaluate the primary and secondary objectives as well as ancillary objective #1. This SAP also applies to the main study manuscript, though not everything specified here will be included in the manuscript.

3.1.5 Analysis Cohort

Intention-to-Treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified. The ITT cohort will likely be the only cohort evaluated at the time of the interim analysis.

As Treated (AT): The AT cohort includes subjects in the ITT cohort but analyzes subjects using the treatment they actually received at the time of their initial procedure. For subjects with a TYRX envelope this means the TYRX envelope remained in the pocket following pocket closure.

modified As Treated (mAT): The mAT cohort includes all subjects and follow-up time in the AT cohort that were successfully implanted with a CIED system (including the TYRX envelope if subject had a successfully placed TYRX envelope) up until the point where a CIED modification (i.e. system modification) occurred. Thus, subjects with a system modification for reasons other than device infection will be considered censored at the time of the system modification.

3.2 Primary Objective

The primary study objective is to compare the rate of major CIED infections through 12 months post-procedure between the TYRX envelope group and the control group (no TYRX envelope).

3.2.1 Hypothesis

The primary study objective will be tested with the following hypothesis:

H₀: $\lambda_{T(t)} = \lambda_{C(t)}$ for all $t \leq 12$ months (365 days), versus

H_a: $\lambda_{T(t)} \neq \lambda_{C(t)}$ for some $t \leq 12$ months (365 days)

where $\lambda_{T(t)}$ is the hazard function for major CIED infection in the TYRX envelope group and $\lambda_{C(t)}$ is the hazard function for major CIED infection in the control group.

3.2.2 Endpoint Definition

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.

Major CIED infections are defined as CIED infections resulting in one or more of the following:

- CIED system removal
- Any invasive procedure (e.g. pocket opened) without system removal
- Treatment with antibiotic therapy if the subject is not a candidate for system removal and infection recurrence after completion of antibiotic therapy or evidence of deep infection with wound dehiscence, erosion, or purulent drainage.
- Death

3.2.3 Performance Requirements

If the hazard ratio : $\lambda_{T(t)}/\lambda_{C(t)}$ is significantly different from 1 (and less than 1), the major infection rate will be considered lower in the TYRX group.

3.2.4 Rationale for Performance Criteria

This study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12 months post-procedure following CIED generator replacement, upgrade, or revision, or the implant of a de novo CRT-D system. The hazard ratio is significantly different if the nominal p-value is less than the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function described above.

3.2.5 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the primary endpoint. The primary method to be used to test the primary objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) the subject is to receive as documented on the randomization eCRF and include treatment as an independent variable. This stratified Cox model assumes that the baseline hazard may be different for each device type, but that the

underlying treatment effect is constant across device type. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if the subject was randomized but no procedure attempt) to: (1) onset date of a subject's first CIED infection meeting the primary endpoint, (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of last follow-up, or (5) 365 days post-procedure. However, if a subject has a major CIED infection during an unsuccessful procedure attempt; days of follow-up will be set to zero. Subjects not meeting the primary endpoint during the follow-up period will be considered censored at the end of their follow-up period as derived above. Based on this statistical test, it will be claimed that the TYRX envelope reduces major CIED infection if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function. Kaplan-Meier plots of freedom from major CIED infection will be presented by treatment group and by treatment group within each device type.

The following sample syntax in SAS will be used to evaluate the primary objective:

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt;
  strata device;
  *different baseline h0 but same HR across device**
run;
```

Sample R-code to fit the stratified Cox model is also displayed below:

```
coxph(Surv(survData$survDays, survData$survStatus)~survData$trt +
strata(survDat$device))
```

If the primary objective is met at either the interim or final analysis time point, the following two assumptions will be tested:

1. Heterogeneity of the hazard ratio across device type:
The following sample syntax in SAS will be used to evaluate the homogeneity of treatment effect across device types for primary objective. If the interaction effect is significant at 0.05 level the treatment effect will not be assumed constant across device type and separate analyses will be performed for each device type.

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt device trt*device;
run;
```

2. Proportional hazards between treatment groups:
The proportional hazards assumption for the treatment effect will be examined graphically by examining plots of the complementary log-log CIED infection free time versus log time. Additionally, an interaction between event time and treatment group will be added to the model. If this interaction term is significant at the 0.05 level then this may provide evidence that the proportional hazards assumption is violated. Should the proportional hazards assumption be violated, inference regarding the effect of the TYRX envelope may be made at several different time points (e.g. 1-month, 6-months, and 12-months post-procedure). The following SAS code implements the test of the proportional hazards assumption:

```

*** PLOT THE COMPLEMENTARY LOG LOG;
proc lifetest data=<data> plot=(s, lls) noprint;
    time time*censor(0);
    strata trt;
    group device;
run;

*** TEST THE TIME VERSUS TREATMENT EFFECT;
proc phreg data=<data>;
    CLASS trt device;
    model eventtime*event(0)=trt trtTime;
    trtTime = trt*log(eventtime);
    strata device;
run;

```

3.2.6 Sample Size

Background

The reported prevalence rate of CIED infection varies widely in the literature and is dependent on the nature of data collection (retrospective vs prospective, single center vs multi-center), CIED infection definition, and population studied. The REPLACE study prospectively evaluated CIED infection requiring system removal or intravenous antibiotics in 1744 subjects undergoing a device replacement or upgrade. The infection rate at 6 months post-procedure for subjects receiving a device replacement was 1.4% and 1.1% for those subjects undergoing a device upgrade.

Analysis of 103,020 device implant claims from Medicare evaluated for Medtronic by Truven Analytics suggested that subsequent invasive procedures related to device infection occurred at a rate of 4.0% for CRT-D, 3.9% for ICDs, and 2.6% for pacemakers through 12-months. The 12-month CIED infection rate associated with replacement devices was 4.1% for CRT-D, 5.4% for ICDs, and 3.4% for pacemakers with 12-month infection rates associated with initial device implants ranging from 4.0% in CRT-Ds to 2.2% in pacemakers. However, examination of CIED infections reported in Medtronic studies, suggests that the Medicare claims data may overestimate the CIED infection rate that may be observed in clinical trials for initial implants by at least 50% (Table 1).

Table 1: 12-Month Infection Rates for Initial Implants by Device Type and Data Source

Device	Data Source	
	Medicare Claims Data 12-Month CIED Infection Rate	Medtronic Studies (12-month CIED Infection Rate (95% CI))
CRT-D	4.1%	2.0% (1.2% =3.4%) ¹
ICD	3.0%	1.5% (0.3% =6.7%) ²
Pacemaker	2.2%	1.2% (0.8% =1.7%) ³

¹Based on 753 subjects with an attempted CRT-D implant in the REVERSE and BLOCK-HF studies.

²Based on 246 subjects from the Model 6947, 6948, and 6949 RV defibrillation lead studies

³Based on 2799 subjects from the 3830, 4074, 5076, Advisa MRI, EnRhythm, EnRhythm MRI, and SAVEPACE studies.

Based on the assumption that the Medicare claims data may overestimate the actual CIED infection rate that may be observed in a clinical trial, it is hypothesized that the 12-month infection rate for initial CRT-D implants, replacement (or upgrade) CRT-D implants, and replacement (or upgrade) ICD implants is 2.4% and is 0.6% for replacement pacemaker implants. Since low power replacement procedures (i.e. pacemaker and CRT-P replacement procedures) will be capped at 25% of the total sample size, an overall 12-month CIED infection rate for the control group is assumed to be 2% for sample size calculation purposes.

Retrospective evidence from the COMMAND study demonstrated that in 624 subjects consecutively implanted with the TYRX envelope the CIED infection rate was 0.48% and ranged from 0% during initial implant procedures to 1.05% during ICD/CRT-D replacement/revision procedures. Additionally, recently published data from Mittal, et. al showed that the CIED infection rate was 1.1% in 275 subjects that received the TYRX envelope compared to 3.6% in 275 propensity matched control subjects over a 6-month period across both low power and high power devices. Finally, early evidence from the CITADEL/CENTURION studies suggests that CIED infection rate among a cohort of 1000 ICD/CRT-D subjects receiving the TYRX envelope is 0.2% at 6-months post-replacement/upgrade; a 9-fold decrease compared to published controls at 6-months. Based on this experience, it is assumed that the TYRX envelope will reduce the risk of CIED infection by 50% through 12-months post-procedure.

Sample Size Calculation

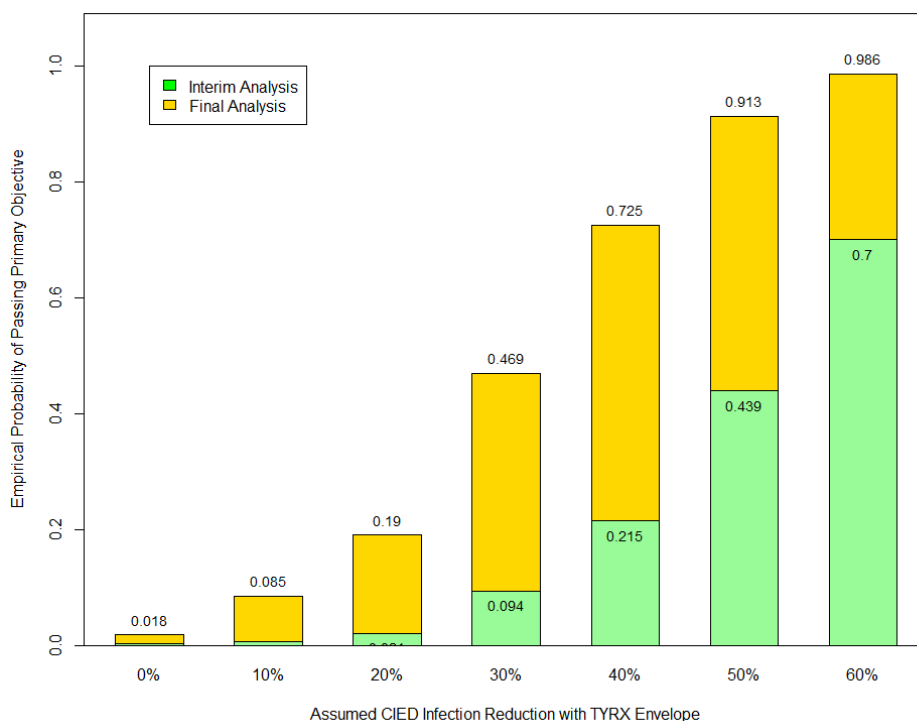
The sample size is derived based on the following assumptions:

1. One-to-one randomization to the TYRX envelope or control group
2. Power to test the primary objective is at least 90%
3. One interim analysis and final analysis
4. The interim analysis will occur when approximately 50% of the statistical information has been accrued
5. One-sided alpha level of 2.5%
6. Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) which approximates O'Brien-Fleming boundaries
7. Assumed control CIED infection rate of 2% at 12-months
 - a. 2.4% for high power (CRT-D/ICD) devices
 - b. 0.6% for low power (pacemaker/CRT-P) devices
 - c. Low power devices are capped at 25% of the required sample size
8. TYRX envelope assumed to reduce the control infection rate by 50%
9. Non-binding futility assessment based on stochastic curtailment at the interim analysis
10. 15% annualized attrition rate that is independent of treatment group and infection status

The method of Lakatos (1988) as implemented in the POWER procedure of SAS v9.2, indicated 6,988 randomized subjects (3,494 randomized to each group) are required to test the primary objective based on the assumptions described above. Thus, up to 7,764 subjects may be enrolled to allow for up to a 10% discontinuation rate between enrollment (i.e. subject consent) and randomization.

A simulation study was performed to confirm the sample size calculation. In addition to the sample size assumptions described above, the simulation assumed that 50% of CIED infections occur within the first month of device procedure. Simulations were performed when the CIED infection risk reduction associated with the TYRX envelope ranged from 0% (null case) to 60%. Figure 1 confirms the sample size calculation and demonstrates that the type I error rate is well controlled. The program used to conduct the simulation analysis is found in section 4.1.

Figure 1: Empirical Power to Test the Primary Objective (n=6,988)



3.2.7 Determination of Subjects' Data for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope the AT or mAT cohorts as described above.

If the primary objective is not met for the ITT cohort, the analysis will be conducted for the AT/mAT cohorts.

3.2.8 Missing Data

The primary analysis cohort will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. Since the primary statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a CIED infection meeting the primary endpoint. The log-rank test will be used to compare the study attrition rate for any reason (study exit or death) between randomized treatment groups to evaluate the pattern of data missingness by treatment group.

Additionally, as many cardiology journals are now requesting sensitivity analyses that include competing risk for death, a competing risks model will be used to test the effect of the TYRX envelope in the presence of competing risk of death unrelated to CIED infection

should the study meet its primary objective. Sample R code for implementing the stratified competing risks model is as follows as recently described by Zhou et. al¹ is provided below:

R syntax below will be used to evaluate treatment effect on CIED infection with consideration of competing risk of death unrelated to CIED infection:

```
Library(crrSC)
Crrs(time, status, cov, strata, failcode=2, cencode=0)

# Status: 0 censor, 1 death unrelated to CIED infection, 2 CIED infection
# Cov: 0 control, 1 envelope
# Strata: low=1 high=2
```

3.2.9 Subgroup analysis

Subgroup analysis will be performed for subjects within high power (CRT=D, ICD) devices and patients with low power (pacemaker, CRT=P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g single chamber to dual chamber, or dual chamber to triple chamber, or low to high power) and patients without device upgrade will be analyzed separately. Additional subgroup analyses may also be performed on a post hoc basis.

The following sample syntax in SAS will be used for the subgroup analysis:

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt;
  by device;
run;
```

Additionally, an interaction between the treatment group and subgroup will be added to the model to test for homogeneity of the treatment effect across subgroups. If this interaction term is significant at the 0.05 level the treatment effect will be considered heterogeneous between subgroups.

```
proc phreg data=<data>;
  CLASS trt subGroup;
  model eventtime*event(0)=trt subgroup trt*subGroup;
run;
```

3.3 Secondary Objectives

The following secondary objectives will be evaluated to gain additional information about the safety and efficacy of the TYRX envelope in the study population. Provided the primary objective of the study is met with a statistically significant p-value, then the secondary objectives will be assessed. The Holm procedure will be used to control the family-wise type I error rate as described in section 3.1.2.6 in order to make statistically valid claims of significance.

¹ B. Zhou, A. Latouche, V. Rocha, J. Fine. 2011. Competing risks regression for stratified data. *Biometrics* 67: 661-670.

3.3.1 Secondary Objective #1

Confirm that the TYRX envelope does not increase the CIED procedure-related or system-related complication rate through 12-months post-procedure.

3.3.1.1 Hypothesis

The first secondary objective will be tested with the following non-inferiority hypothesis:

$H_0: \lambda_T(t)/\lambda_c(t) \geq 1.33$ for $t \leq 12$ months (365 days), versus

$H_a: \lambda_T(t)/\lambda_c(t) < 1.33$ for $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for CIED system-or procedure-related complications in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for CIED system-related complications in the control group. Rejecting the null hypothesis would indicate that the TYRX envelope does not increase the CIED system-or procedure-related complication rate by more than 33% on a relative scale or 4.4% on a linear scale when the underlying CIED system or procedure complication freedom rate at 12-months is 85%.

3.3.1.2 Endpoint

A CIED system-related complication is defined as an adverse event that meets the complication definition as determined by the CEC and is considered by the CEC to be related to one of the implanted CIED system components (i.e. device, RV lead, RA lead, LV lead, other lead, or the TYRX envelope).

A CIED procedure-related complication is defined as an adverse event that meets the complication definition as determined by the CEC and is considered by the CEC to be related to the CIED procedure (i.e. replacement/upgrade/new implant/revision) or a system modification including the TYRX envelope (if applicable).

3.3.1.3 Analysis Methods

All potential adverse events potentially related to the implanted system (i.e. device, leads), the TYRX envelope, or the CIED replacement/upgrade/implant or system modification procedure will be reported on the eCRFs as they occur. The CEC will adjudicate each reported adverse event for its relationship to the CIED system and CIED procedure. Additionally, the CEC will classify each CIED system-related or procedure-related adverse event as a complication or observation. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject was randomized but not implanted) to: (1) onset date of a subject's first CIED system related or procedure related complication (including the TYRX envelope where applicable), (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of last follow-up, or (5) 365 days post-procedure. Subjects with a procedure-and/or system-related complication occurring prior to their last CIED procedure attempt will their event date set to day zero. Subjects not having a CIED system-related or procedure-related complication during the follow-up period will be considered censored on the day as derived above.

The effect of the TYRX envelope on the rate of CIED system-or procedure-related complications will be tested using a Cox proportional hazards regression model stratified by device type (low power versus high power) containing an indicator term for treatment group. The observed hazard ratio from the Cox model will be compared to the non-

inferiority margin of 1.33. The null hypothesis will be rejected in favor of the alternative and the TYRX envelope will be considered non-inferior to the control group if the p-value computed from the non-inferiority test is less than the type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons. Kaplan-Meier plots of freedom from system- or procedure-related complications will be presented by treatment group and by treatment group within each device type.

The following sample syntax in SAS will be used to evaluate the second objective #1:

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt;
  estimate trt 1/testvalue=0.285 lower;  **ln(1.33)=0.285**
  strata device;
run;
```

If secondary objective #1 is met at either the interim or final analysis time point, the following two assumptions will be tested in an analogous fashion as described for the primary objective:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.3.1.4 Power to test the objective

Background

Table 2 displays the procedure- or system-related complication rates from several Medtronic and non-Medtronic sponsored studies. These data indicate that complications related to the implanted system (i.e. device and leads) or procedure range from 4.0% to 24.7% depending on complication definition, devices studied, and study population. Based on these data it appears reasonable based on the mix of devices and population under investigation in the WRAP-T study that the underlying system or procedure complication free rate could range from 80% to 90% at 12-months post-procedure.

Table 2: System or Procedure-Related Complications Reported Previous Studies

Study	Devices Studied	Population	Time Frame	Complication Rate (95% CI)
Gould et. al 2008 ¹	ICD (n=451)	Replacements	12=months	9.1% (NR)
REPLACE ²	IPG (n=515) ICD (n=327) CRT=D (n=175) CRT=P (n=14)	Replacements	6=months	4.0% (2.9%=5.4%)
REPLACE	IPG (n=329) ICD (n=320) CRT=D (n=49) CRT=P (n=15)	Upgrades	6=months	15.3% (12.7% =18.1%)
BLOCK=HF	CRT=D (n=230)	New Implants	12=months	22.9% (18.0% =29.0%)
BLOCK=HF	CRT=P (n=531)	New Implants	12=months	17.7% (14.7% =21.3%)
REVERSE	CRT=D (n=523)	New Implants	12=months	17.0% (14.0% =20.5%)
REVERSE	CRT=P (n=104)	New Implants	12=months	24.7% (17.5% =34.4%)
4074 Study	IPG (n=132)	New Implants	6=months	13.9% (9.0% =21.1%)
EnRhythm MRI ³	IPG (n=469)	New Implants	12=months	11.3% (8.8% =14.6%)
Advisa MRI ³	IPG (n=269)	New Implants	6=months	9.2% (6.3% =13.4%)

¹Gould et. al. 2008. Heart Rhythm 5: 1675=1681. Major complication defined as post=operative death, nonfatal MI, cardiogenic shock, or event requiring reoperation.

²Poole et. al. 2010. Circulation 122:1553=1561. Major complications defined as an event defined in Table 1 of the manuscript. In general major complications required invasive intervention.

³Does not include system complications related to the RA lead only.

Power Calculation

Since the primary objective of the study dictates the sample size for the study, the power to test this secondary objective under several scenarios was determined based on the method of Lakatos as implemented in PASS 2008. The following assumptions were made in the power calculation:

1. Sample size of 6,988 subjects randomized 1:1 to the TYRX envelope or control group
2. One interim analysis and final analysis
3. The interim analysis will occur when approximately 50% of the follow=up is accrued
4. One= sided alpha level of 2.5%
5. Hwang=Shih=DeCani alpha spending function with a gamma parameter of negative 4 (=4) which approximates O'Brien=Fleming boundaries and means the final test will be conducted at a one= sided alpha=level of 0.0238 which is analogous to a two= sided alpha level of 0.0476.
6. 15% annualized attrition rate that is independent of treatment group and system= related complication
7. 12=month system=or procedure=related complication rate in the control group could range from 10% to 20%
8. The TYRX envelope has no effect on the system=or procedure=related complication rate
9. Non=inferiority margin of 33% on a relative scale or 4.4% on a linear scale when the underlying CIED system complication freedom rate at 12=months is 85%

Table 3 indicates that the statistical power to test the non=inferiority hypothesis associated with secondary objective #1 is greater than 94% based on the assumptions above across a range of plausible control group event rates.

Table 3: Power to Test Secondary Objective #1 with Sample Size of 6,988 Subjects

12-month system-related Complication Free Rate	Control Group Hazard Rate	Non-inferiority Margin (Relative Scale)	Non-inferiority Margin (Linear Scale) ¹	Power
90%	0.1054	1.33	3.1%	94.9%
88%	0.1278		3.6%	97.6%
86%	0.1508		4.2%	98.9%
85%	0.1625		4.4%	99.3%
84%	0.1744		4.7%	99.5%
82%	0.1985		5.2%	99.8%
80%	0.2231		5.7%	99.9%

¹The non-inferiority margin on the linear scale is defined as the difference in the survival curves for the event rate at 12-months post-randomization between the control group and the TYRX™ Absorbable Antibacterial Envelope group.

3.3.1.5 Determination of Subjects' Data for Analysis

Since non-inferiority tests based on intention-to-treat principles may be anti-conservative, the results of the non-inferiority test will be reported for both the ITT and AT cohorts as recently suggested². However, statistical inference for this objective will be based on the AT cohort. All randomized subjects and all follow-up from randomized subjects is included in the ITT cohort regardless of treatment received. For the AT cohort, all follow-up from all subjects will be included, but the analysis will be based on the treatment the subject actually received at the time of their original CIED procedure.

3.3.1.6 Missing Data

The analysis cohorts will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. Since the statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a CIED system-or procedure-related complication. As described in section 3.2.8 the log-rank test will be used to compare the study attrition rate for any reason between randomized treatment groups to evaluate the pattern of data missingness.

3.3.1.7 Subgroup Analyses

Subgroup analysis will be performed for subjects within high power (CRT-D, ICD) devices and patients with low power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g single chamber to dual chamber, or dual chamber to triple chamber, or lower to high power) and patients without device upgrade will be analyzed separately using the methods described in section 3.2.9.

3.3.2 Secondary Objective #2

Compare the major CIED infection rate during the entire follow-up between the TYRX envelope group and the control group.

² Head, SJ et al. 2012. Non-inferiority study designs: lessons to be learned from cardiovascular trials. *European Heart Journal* 33(11): 1318-1325.

3.3.2.1 Hypothesis

The second secondary objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_C(t)$ for all $t \leq T$, versus

$H_a: \lambda_T(t) \neq \lambda_C(t)$ for some $t \leq T$

where $\lambda_T(t)$ is the hazard function for major CIED infection in the TYRX envelope group and $\lambda_C(t)$ is the hazard function for major CIED infection in the control group during the entire follow-up period.

3.3.2.2 Endpoint Definition

Major CIED infection is defined in section 3.2.2.

3.3.2.3 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the major CIED infection definition. The primary method to be used to test this objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject was randomized but not implanted) to: (1) onset date of a subject's first CIED infection meeting the primary endpoint, (2) study exit date (if exited), (3) date of death (if death occurs), or, (5) date of last follow-up. Subjects who meet the endpoint prior to their last CIED procedure attempt will be considered to have met the endpoint on day zero. Subjects not having a major CIED infection during the follow-up period will be considered censored at their last follow-up day. Based on this statistical test, it will be claimed that the TYRX envelope reduces major CIED infection during the entire study period if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons. Kaplan-Meier plots of freedom from major CIED infection will be presented by treatment group and by treatment group within each device type.

The SAS code for implementing the stratified Cox regression model will be similar to the sample code described in 3.2.5.

If secondary objective #2 is met at either the interim or final analysis time point, the following two assumptions will be tested as described above:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.3.2.4 Determination of Subjects' Data for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

If the objective is not met for the ITT cohort, the analysis will be conducted for the AT/mAT cohorts.

3.3.2.5 Missing Data

The primary analysis cohort for this objective will include all follow-up from all randomized subjects through the end of the study or visit cutoff for the interim analysis (i.e. Intention-to-Treat principle). Since the statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the end of the study (or visit cutoff) without experiencing a major CIED infection. The log-rank test will be used to compare the study attrition rate for any reason (study exit or death) between randomized treatment groups to evaluate the pattern of data missingness by treatment group.

Additionally, a competing risks model will be used to test the effect of the TYRX envelope in the presence of the competing risk of death unrelated to CIED infection should this objective be met as described in section 3.2.8.

3.3.2.6 Subgroup Analyses

Subgroup analysis will be performed for subjects within high power (CRT-D, ICD) devices and patients with low power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g single chamber to dual chamber, or dual chamber to triple chamber, or low to high power) and subjects without device upgrade will be analyzed separately using the methods described in section 3.2.9.

3.3.3 Secondary Objective #3

Compare the rate of major and minor CIED infections through 12-months post-procedure between the TYRX envelope group and the control group.

3.3.3.1 Hypothesis

The third secondary objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_c(t)$ for all $t \leq 12$ months (365 days), versus

$H_a: \lambda_T(t) \neq \lambda_c(t)$ for some $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for major and minor CIED infection in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for major and minor CIED infection in the control group.

3.3.3.2 Endpoint Definition

CIED infections, including major CIED infections are defined in section 3.2.2. Minor CIED infections are CIED infections that are not classified as major CIED infections.

3.3.3.3 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the major CIED infection definition. Those infections related to the CIED that do not meet the major CIED infection will be considered minor CIED infections. The primary method to be used to test this objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject is randomized but not implanted) to: (1) onset date of a subject's first major or minor CIED infection, (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of last follow-up, or (5) 365 days post-procedure. Subjects who meet the endpoint prior to their last CIED procedure attempt will be considered to have met the endpoint on day zero. Subjects not having a major or minor CIED infection during the follow-up period will be considered censored on the day as derived above. Based on this statistical test, it will be claimed that the TYRX envelope reduces major or minor CIED infection if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons. Kaplan-Meier plots of freedom from major or minor CIED infection will be presented by treatment group and by treatment group within each device type.

The SAS code for implementing the stratified Cox regression model will be similar to the sample code described in 3.2.5.

If secondary objective #3 is met at either the interim or final analysis time point, the following two assumptions will be tested as described above:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.3.3.4 Determination of Subjects' Data for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

If the objective is not met for the ITT cohort, the analysis will be conducted for the AT/mAT cohorts.

3.3.3.5 Missing Data

The primary analysis cohort for this objective will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. Since the statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a major or minor CIED infection. The log-rank test will be used to compare the study attrition rate for any reason

(study exit or death) between randomized treatment groups to evaluate the pattern of data missingness by treatment group.

Additionally, a competing risks model will be used to test the effect of the TYRX envelope in the presence of the competing risk of death unrelated to CIED infection should this objective be met as described in section 3.2.8.

3.3.3.6 Subgroup Analyses

Subgroup analysis will be performed for subjects within high-power (CRT-D, ICD) devices and subjects with low-power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g. single chamber to dual chamber, or dual chamber to triple chamber, or low to high power) and subjects without device upgrade will be analyzed separately using the methods described in section 3.2.9.

3.4 Ancillary Objectives

The following ancillary objectives are intended to gain additional information about the performance of the TYRX envelope. The type I error rate is not controlled for the ancillary objectives. Not all ancillary objectives may be evaluated if the study's primary objective is not met.

3.4.1 Ancillary Objective #1: Mortality

To compare all-cause mortality rates between the TYRX envelope group and the control group.

3.4.1.1 Endpoint

Death for any cause

3.4.1.2 Hypothesis

This ancillary objective will be tested with the following hypothesis:

$H_0: \lambda_T(t) = \lambda_c(t)$ for all $t \leq T$, versus

$H_a: \lambda_T(t) \neq \lambda_c(t)$ for some $t \leq T$

where $\lambda_T(t)$ is the hazard function for death for any cause in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for death any cause in the control group during the entire follow-up period.

3.4.1.3 Analysis Methods

The primary method to be used to evaluate the hypothesis above will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject was randomized but not implanted) to the (1) date of death or (2) last study contact date. Subjects alive at their last follow-up day will be censored on their last day as derived above. A p-value less than 0.05 will be considered statistically

significant. Kaplan-Meier plots of subject survival will be presented by treatment group and by treatment group within each device type.

The SAS code for implementing the stratified Cox regression model will be similar to the sample code described in 3.2.5

If ancillary objective #1 is met at either the interim or final analysis time point, the following two assumptions will be tested as described above:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.4.1.4 Determination of Subjects for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

If the objective is not met for the ITT cohort, the analysis will be conducted for the AT cohort.

3.4.2 Ancillary Objective #2: CIED procedure success rate

Evaluate the CIED procedure success rate in the TYRX envelope group and the control group

3.4.2.1 Analysis Methods

Information related to the CIED procedure (i.e. initial implant or index replacement/upgrade or index system revision) will be collected on the procedure eCRF. A procedure attempt is defined as any CIED procedure where the device pocket is opened or venous access was gained (i.e. skin was cut). A successful procedure is defined as an implant attempt where the device is successfully connected to the system's leads and the CIED system remains in the body and the device pocket is closed. Additionally, for those subjects randomized to the TYRX envelope group, the TYRX envelope must also remain in the device pocket following pocket closure to qualify as a successful CIED procedure.

Specifically, for all subjects with a procedure attempt a CIED procedure can only be considered successful if the question on the procedure CRF "Was a generator in the pocket following the procedure?" is answered as "Yes". Additionally, for those subjects randomized to the TYRX envelope group, the question "Was the TYRX envelope in the device pocket following the implant procedure?" must also be answered as "Yes". Note that for purposes of determining procedure success, subjects with a CRT device where the LV lead cannot be placed adequately may still be considered a success if the generator remains in the pocket. In these cases, a system modification form would be required if another LV lead implant attempt is made during a separate procedure.

The CIED procedure success rate will be defined on a per subject basis as the number of subjects with their last CIED procedure considered successful divided by the number of subjects with at least one CIED procedure attempt. Fisher's exact test will be used to compare the procedure success rate between the TYRX envelope group and the control group.

The following sample syntax in SAS will be used to evaluate the ancillary objective #2:

```
proc freq;
  tables trt*success /exact cmh;
  weight count;
run;
```

Fisher's exact test will also be used to compare the percentage of subjects with more than one procedure attempt (i.e. more than one CIED procedure CRF) by randomized treatment group. For each randomized treatment group the denominator will be the number of subjects with a successful procedure and the numerator will be the number of subjects with a successful procedure requiring more than one procedure to obtain the successful procedure.

3.4.2.2 *Determination of Data for Analysis*

Data from all randomized subjects with a CIED procedure attempt will be included in the analysis. The primary analysis cohort will be the ITT population with the additional requirement that the subject must have a CIED procedure attempt.

3.4.3 Ancillary Objective #3: Summarize adverse events

To summarize adverse events by treatment group

3.4.3.1 *Analysis Methods*

Subjects will be queried for AEs at all scheduled and unscheduled visits. All AEs potentially related to the CIED system, CIED implant or system modification procedure, and all SAEs regardless of their relationship to the CIED system or CIED procedure (including the TYRX envelope if applicable) will be collected. Medtronic safety specialists will ensure that at a minimum all AEs that are potentially related to the CIED system (including the TYRX envelope), or CIED procedure, or death are classified by the CEC. Summary tables will be compiled categorizing the AEs with respect to procedure relatedness, CIED relatedness (including CIED component), and TYRX envelope relatedness. For events classified by the CEC, the CEC classification will be used in the analysis. In cases where only the investigator classifies the event, the investigator's classification will be used. In addition, the number of events and number of subjects with events by MedDRA term will be displayed. Additionally, the nominal p-value from the log-rank test will be used to identify system- or procedure-related AEs occurring on or after a CIED procedure attempt by MedDRA preferred term that may differ between treatment groups. This test does not protect the type I error, but may help identify specific AEs that differ between randomized treatment group for further evaluation. These tests will only be performed for preferred terms that occur in more than five subjects.

3.4.3.2 *Determination of Data for Analysis*

All adverse events collected during the study will be included in this analysis.

3.4.4 Ancillary Objective #4: Predictors of CIED infection

To identify predictors of major CIED infection

3.4.4.1 Analysis Methods

Subject demographics and medical history including previous device history will be collected at baseline. CIED procedure-related variables such as antibiotic prophylaxis, surgical site preparation, procedure duration, device type, and number of leads will be collected for each CIED procedure. Additionally, device characteristics such as impedance, optivol fluid status, and heart rate variability etc. will be collected via device interrogations at each follow-up visit. Cox regression models will be employed using subjects in the control group to identify factors that may be associated with major CIED infection. Additionally, multivariable Cox models may be used to develop a risk model for major CIED infection. For any such multivariable Cox model, the number of degrees of freedom available and hence the number of candidate predictors available (and their functional form) for modelling will be determined by the number of major CIED infections in the control group. This analysis will be exploratory in nature.

3.4.4.2 Determination of Data for Analysis

All subjects randomized to the control group with a CIED procedure attempt who do not receive the TYRX envelope during their CIED procedure.

3.4.5 Ancillary Objective #5: Quality of Life

Summarize quality of life.

3.4.5.1 Analysis Methods

Subjects will be asked to complete the EQ-5D questionnaires at baseline and at the 12-month visit (or study exit if the subject exits the study for reasons other than lost to follow-up prior to completing the 12-month visit). Additionally, subjects with a CIED infection will be asked to complete the EQ-5D within two weeks following their CIED infection diagnosis and at 1-month, 3-months, and 6-months post-CIED infection diagnosis.

The EQ-5D summary health score is calculated based on five “dimension” questions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For subjects completing the EQ-5D-3L questionnaire (primarily OUS subjects) each dimension has three options, which are in general: 1=no problem, 2=some problem, 3=extreme problem. For subjects completing the EQ-5D-5L questionnaire (primarily US subjects) each dimension has five options which are in general: 1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, 5=unable to perform.

For purposes of the final study report, EQ-5D summary scores will be standardized to the EQ-5D-3L summary health score using EQ-5D-5L to EQ-5D-3L crosswalk value set current at the time the final report is prepared, unless EQ-5D-5L value sets become available from EuroQoL during the WRAP-IT study for geographies using the EQ-5D-5L.

Each subject’s summary health score will be standardized to the same country value set (e.g. US) regardless of the subject’s origin using the appropriate EQ-5D-3L value set.

Medtronic’s healthcare economics group may request additional summaries of the EQ-5D data following study completion for conducting cost effectiveness analyses described in the healthcare economics analysis plan.

Descriptive statistics will be used to summarize the change in EQ-5D scores from baseline to the 12-month visit by infection status. Additionally, the changes in EQ-5D between CIED infection and post-CIED infection will be computed using summary statistics for all subjects with a major CIED infection as classified by the CEC. More detailed analysis methods will be described in the health economics Statistical Analysis Plan.

Bar charts will be used to present results from the EQ-5D descriptive system as a health profile. Summary health score will be presented in tables similar to shown below:

EQ-5D		Baseline				12-months				Change		
		N	Mean ± Std.	Median	Range	N	Mean ± Std.	Median	Range	N	Mean ± Std.	95% CI
EQ-5D Health Score	Infection											
	No Infection											
EQ-5D Visual Analog Scale	Infection											
	No Infection											

3.4.5.2 Determination of Data for Analysis

Completed EQ-5D questionnaires from all randomized subjects will be used to describe the changes in EQ-5D score from baseline. All completed EQ-5D questionnaires following an adjudicated CIED infection will be used to summarize the change in EQ-5D score from baseline following CIED infection.

3.4.6 Ancillary Objective #6: Healthcare System Cost Effectiveness

Objective

To assess the cost-effectiveness of the TYRX envelope.

Analysis Methods

Health care utilizations (HCUs) related to suspected CIED infection will be collected on the eCRFs. HCUs related to CIED infection include all hospitalizations, emergency department visits, urgent care, or unscheduled follow-up visits associated with the suspected CIED infection regardless of location of care.

For each major CIED infection as classified by the CEC, the following information will be compiled and provided to Medtronic's healthcare economics group:

- Subject identifier, randomized treatment group, and treatment actually received
- For each inpatient hospitalization the hospitalization admission date, discharge date, total hours in ICU, and total hours in cardiac ward
- For each outpatient visit the type of outpatient visit, provider type, and visit date
- Date and type of any long-term health care facility stay
- Start date, stop date, frequency per week, and frequency per day for each session of home health care
- Medications used to treat the CIED infection as recorded on the AE eCRF associated with the major CIED infection

Additionally, the following health care utilization information related to major CIED infections will be summarized and compared between randomized treatment groups using proportional odds models:

- Total days hospitalized for major CIED infection
- Total ICU hours (1 day = 24 hours) for major CIED infection
- Total hours (1 day = 24 hours) in cardiac ward for major CIED infection
- Days in long-term health-care facility for major CIED infection

```
Proc logistic data=<data> order=<order>;
  Class trt (param=ref ref='0');
  model nDays(ascending) = trt logFupDays;
run;
*** trt=1 for ENVELOPE and trt=0 for NO ENVELOPE;
```

The following health care utilization information related to major CIED infections will be summarized and compared between randomized treatment groups using negative binomial regression models:

- Total number of outpatient visits for major CIED infection
-
- Number of home health care visits for major CIED infection

Each negative binomial regression model will include the number of days (or hours) of subject follow-up as the offset, randomized treatment group as the independent variable, and parameter of interest as the dependent variable. Subjects without a major CIED infection will be considered to have 0 days (or hours) of the parameter of interest. The following sample SAS code implements the negative binomial regression model described above:

```
proc genmod data=<data>
  model nEvent = trt / dist=nb link=log offset=logFUPdays;
run;
*** trt=1 for ENVELOPE and trt=0 for NO ENVELOPE;
```

Additionally, the cost incurred from each major CIED infection will be based on the actions taken to address each major CIED infection. The total cost of major CIED infections observed in the study will be compared to the total cost incurred by adding the TYRX envelope to the CIED procedure. Economic models will be employed to quantify the cost savings and/or cost-effectiveness of the TYRX envelope. The decision-analytic framework of any potential economic model will be detailed in the health economics analysis plan. Medtronic's healthcare economics group will be primarily responsible for the cost effectiveness analysis but will likely request study data from the WRAP-T study's statistical staff for their work.

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4 APPENDIX

4.1 Sample Size Simulation Program

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4.2 Information Fraction Simulation Program

The following R program can be used to calculate the information fraction via simulation at the interim analysis

```
[REDACTED R CODE]
```

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Amendment 1 to the WRAP-IT Statistical Analysis Plan	
<i>Clinical Investigation Plan Title</i>	World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT)
<i>Sponsor/Local Sponsor</i>	Medtronic, Inc 8200 Coral Sea St NE Mounds View, MN USA 55112 1-800-328-2518 Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands (+31)-43-35-66-566 Medtronic Australasia Pty Ltd 97 Waterloo Rd, North Ryde 2113 PO Box 945, North Ryde Australia, 1670 (+61)-2-9857-9000 Medtronic Latin America HQ Medtronic USA, Inc., Doral Corporate Center II 3750 NW 87th Avenue, Suite 700 Miami, FL U.S.A. 33178 (+1)-305-500-9328 India Medtronic Pvt. Ltd. 1241, Solitaire Corporate Park, Building No 12, 4th Floor, Andheri-Ghatkopar Link Road, Andheri (E), Mumbai MH 400093 India (+91)-22-33074700-1/2/3 Medtronic International Ltd. 1101-06, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong Hong Kong SAR, China (+852)-2919-1300

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<i>Document Version</i>	Version 1.0
<i>Document Reference Number</i>	NA
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	<ul style="list-style-type: none">Initial Release	Kurt Stromberg, Senior Principal Statistician

2. Introduction

2.1. Purpose

The purpose of the amendment to version 1.0 of the WRAP-IT Statistical Analysis Plan (SAP) is to document any modifications to the WRAP-IT SAP that were made following the interim analysis, but prior to breaking the blind for the final analysis. The primary purpose of this amendment is to further clarify specific sections in the WRAP-IT SAP. The remainder of WRAP-IT SAP version 1.0 was unchanged.

3. Specific Changes

3.1. Definition of the As-Treated Cohort

3.1.1. Original Text from WRAP-IT SAP version 1.0

As Treated (AT): The AT cohort includes subjects in the ITT cohort but analyzes subjects using the treatment they actually received at the time of their initial procedure. For subjects with a TYRX envelope this means the TYRX envelope remained in the pocket following pocket closure.

3.1.2. Rationale for Change

The original text in version 1.0 of the WRAP-IT SAP was unclear as to whether subjects without a procedure attempt or with no successful procedure attempts would be included in the AT cohort. Additionally, the original text did not indicate whether the analysis of the AT cohort would stratify by the device type (high power or low power) as randomized or by the device type as actually implanted.

3.1.3. Amended Text

As Treated (AT): The AT cohort includes subjects in the ITT cohort but will be defined using the treatment actually received at the time of their final index procedure. Randomized subjects without a procedure attempt and randomized subjects without a device remaining in the pocket at their final index procedure will be excluded from the AT cohort. Thus the number of subjects in the AT cohort will be less than the number of subjects in the ITT cohort. Furthermore, subjects with a device and *with* a TYRX envelope remaining in the device pocket following their procedure will be considered members of the TYRX group in the AT cohort regardless of randomization assignment. Similarly, subjects with a device,

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but *without* a TYRX envelope in their device pocket following procedure will be considered members of the control group in the AT cohort regardless of randomization assignment.

For analyses stratified by device class (high power or low power) the analyses will stratify by the device class received at the index procedure implant unless the device class is unknown (e.g., device not manufactured by Medtronic) in which case the device class as randomized will be used.

3.2. Definition of Analysis Cohort for Ancillary Objective #2 (CIED Procedure Success)

3.2.1. Original Text from WRAP-IT SAP version 1.0

Information related to the CIED procedure (i.e. initial implant or index replacement/upgrade or index system revision) will be collected on the procedure eCRF. A procedure attempt is defined as any CIED procedure where the device pocket is opened or venous access was gained (i.e. skin was cut). A successful procedure is defined as an implant attempt where the device is successfully connected to the system's leads and the CIED system remains in the body and the device pocket is closed. Additionally, for those subjects randomized to the TYRX envelope group, the TYRX envelope must also remain in the device pocket following pocket closure to qualify as a successful CIED procedure.

Specifically, for all subjects with a procedure attempt, a CIED procedure can only be considered successful if the question on the procedure CRF "Was a generator in the pocket following the procedure?" is answered as "Yes". Additionally, for those subjects randomized to the TYRX envelope group, the question "Was the TYRX envelope in the device pocket following the implant procedure?" must also be answered as "Yes". Note that for purposes of determining procedure success, subjects with a CRT device where the LV lead cannot be placed adequately may still be considered a success if the generator remains in the pocket. In these cases, a system modification form would be required if another LV lead implant attempt is made during a separate procedure.

The CIED procedure success rate will be defined on a per subject basis as the number of subjects with their last CIED procedure considered successful divided by the number of subjects with at least one CIED procedure attempt. Fisher's exact test will be used to compare the procedure success rate between the TYRX envelope group and the control group. Data from all randomized subjects with a CIED procedure attempt will be included in the analysis. The primary analysis cohort will be the ITT population with the additional requirement that the subject must have a CIED procedure attempt.

Determination of Subjects for Analysis

Data from all randomized subjects with a CIED procedure attempt will be included in the analysis. The primary analysis cohort will be the ITT population with the additional requirement that the subject must have a CIED procedure attempt.

3.2.2. Rationale for Change

The DMC informed Medtronic on 25 February 2017 that Medtronic may want to consider revising the analysis cohort for the analysis of the procedure success rate (ancillary objective #2), as several subjects randomized to the TYRX envelope group never had a TYRX envelope implant attempt. Reasons for not having a TYRX envelope implant attempt included "TYRX envelope inventory issues" and "study site error".

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3.2.3. Amended Text

Information related to the CIED procedure (i.e., initial implant or index replacement/upgrade or index system revision) will be collected on the procedure eCRF. A procedure attempt is defined as any CIED procedure where the device pocket is opened or venous access was gained (i.e., skin was cut). A successful procedure is defined as an implant attempt where the device is successfully connected to the system's leads and the CIED system remains in the body and the device pocket is closed. Additionally, for those subjects randomized to the TYRX envelope group, the TYRX envelope must also remain in the device pocket following pocket closure to qualify as a successful CIED procedure.

Specifically, for all subjects with a procedure attempt, a CIED procedure can only be considered successful if the question on the procedure CRF "Was a generator in the pocket following the procedure?" is answered as "Yes". Additionally, for those subjects randomized to the TYRX envelope group *and with an attempted implant of the TYRX envelope*, the question "Was the TYRX envelope in the device pocket following the implant procedure?" must also be answered as "Yes". Note that for purposes of determining procedure success, subjects with a CRT device where the LV lead cannot be placed adequately may still be considered a success if the generator remains in the pocket. In these cases, a system modification form would be required if another LV lead implant attempt is made during a separate procedure.

The CIED procedure success rate will be defined on a per subject basis as the number of subjects with their last CIED procedure considered successful divided by the number of subjects with at least one CIED procedure attempt. Fisher's exact test will be used to compare the procedure success rate between the TYRX envelope group and the control group.

Determination of Subjects for Analysis

The primary analysis cohort will be the ITT population with the following additional requirements:

1. A subject must have a CIED procedure attempt (e.g., skin cut)
2. Subjects randomized to the TYRX group must have had an attempt to implant the TYRX envelope. Specifically, subjects who crossed over to the control group without an attempted TYRX envelope implant were excluded from this analysis. For example, this includes subjects who were crossed over due to TYRX inventory issues or site error.
3. Subjects randomized to the control group that crossed over to the TYRX envelope group during their implant attempt will be conservatively excluded from the analysis cohort for this objective since it is not possible to accurately determine the number of control group subjects with an attempted crossover to the TYRX envelope group where the TYRX envelope was not successfully implanted.

3.3. Analysis Methods for Ancillary Objective #6: (Healthcare System Cost Effectiveness)

3.3.1. Original Text from WRAP-IT SAP version 1.0

Analysis Methods

Health care utilizations (HCUs) related to suspected CIED infection will be collected on the eCRFs. HCUs related to CIED infection include all hospitalizations, emergency department visits, urgent care, or unscheduled follow-up visits associated with the suspected CIED infection regardless of location of care.

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For each major CIED infection as classified by the CEC, the following information will be compiled and provided to Medtronic's healthcare economics group:

- Subject identifier, randomized treatment group, and treatment actually received
- For each inpatient hospitalization the hospitalization admission date, discharge date, total hours in ICU, and total hours in cardiac ward
- For each outpatient visit the type of outpatient visit, provider type, and visit date
- Date and type of any long-term health care facility stay
- Start date, stop date, frequency per week, and frequency per day for each session of home health care
- Medications used to treat the CIED infection as recorded on the AE eCRF associated with the major CIED infection

Additionally, the following health care utilization information related to major CIED infections will be summarized and compared between randomized treatment groups using proportional odds models:

- Total days hospitalized for major CIED infection
- Total ICU hours (1 day = 24 hours) for major CIED infection
- Total hours (1 day = 24 hours) in cardiac ward for major CIED infection
- Days in long-term health-care facility for major CIED infection

```
Proc logistic data=<data> order=<order>;  
  Class trt (param=ref ref='0');  
  model nDays(ascending) = trt logFupDays;  
run;  
*** trt=1 for ENVELOPE and trt=0 for NO ENVELOPE;
```

The following health care utilization information related to major CIED infections will be summarized and compared between randomized treatment groups using negative binomial regression models:

- Total number of outpatient visits for major CIED infection
- Number of home health care visits for major CIED infection

Each negative binomial regression model will include the number of days (or hours) of subject follow-up as the offset, randomized treatment group as the independent variable, and parameter of interest as the dependent variable. Subjects without a major CIED infection will be considered to have 0 days (or hours) of the parameter of interest. The following sample SAS code implements the negative binomial regression model described above:

```
proc genmod data=<data>  
  model nEvent = trt / dist=nb link=log offset=logFUPdays;  
run;  
*** trt=1 for ENVELOPE and trt=0 for NO ENVELOPE;
```

Additionally, the cost incurred from each major CIED infection will be based on the actions taken to address each major CIED infection. The total cost of major CIED infections observed in the study will be compared to the total cost incurred by adding the TYRX envelope to the CIED procedure. Economic models will be employed to quantify the cost savings and/or cost-effectiveness of the TYRX envelope. The decision-analytic framework of any potential economic model will be detailed in the health economics

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analysis plan. Medtronic's healthcare economics group will be primarily responsible for the cost effectiveness analysis but will likely request study data from the WRAP-IT study's statistical staff for their work.

3.3.2. Rationale for Change

There were two reasons for modifying the original text in version 1.0 of the WRAP-IT SAP.

First, the blinded study statistician noticed that the distribution of healthcare utilization parameters had many more zeros (i.e., subjects with value of zero for healthcare utilization parameter) than could be accommodated by a negative binomial distribution. Specifically, the distribution of these variables was highly zero inflated. Thus, it was necessary to change from the originally specified negative binomial model to a negative binomial hurdle model to account for the zero inflation.

Secondly, the healthcare cost effectiveness analyses are being specified in the healthcare economics analysis plan. Moreover, since many of the healthcare cost effectiveness analyses will likely occur following distribution of the WRAP-IT final clinical study report, it was necessary to identify which healthcare utilization analyses would appear in the final report.

3.3.3. Amended Text

Analysis Methods

Health care utilizations (HCUs) related to suspected CIED infection will be collected on the eCRFs. HCUs related to CIED infection include all hospitalizations, emergency department visits, urgent care, or unscheduled follow-up visits associated with the suspected CIED infection regardless of location of care.

For each major CIED infection as classified by the CEC, the following information will be compiled and provided to Medtronic's healthcare economics group:

- Subject identifier, randomized treatment group, and treatment actually received
- For each inpatient hospitalization the hospitalization admission date, discharge date, total hours in ICU, and total hours in cardiac ward
- For each outpatient visit the type of outpatient visit, provider type, and visit date
- Date and type of any long-term health care facility stay
- Start date, stop date, frequency per week, and frequency per day for each session of home health care
- Medications used to treat the CIED infection as recorded on the AE eCRF associated with the major CIED infection

Medtronic's healthcare economics group (or their designees) will use this information to evaluate the cost-effectiveness of the TYRX envelope and develop subsequent ancillary study publications. The methodology for the cost-effectiveness models is detailed in the WRAP-IT health economics analysis plan.

For purposes of the final report, the following healthcare utilization parameters will be summarized by randomized treatment group for subjects with a major CIED infection within 12-months, major CIED infection during the entire follow-up period, any major or minor CIED infection within 12-months, and any major or minor CIED infection during the entire follow-up period:

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- Total days hospitalized for hospitalizations exceeding 24 hours
- Days in intensive care unit (24 hours = 1 day and fractional days rounded up)
- Days in cardiac ward (24 hours = 1 day and fractional days rounded up)
- Total days hospitalized for hospitalization less than 24 hours
- Number of emergency department visits
- Number of urgent clinic visits
- Number of clinic visits

For each healthcare utilization parameter, the rate of healthcare contacts per year (e.g., hospitalized days per year, number of emergency department visits) in each randomized treatment group will be computed by dividing the total number of contacts by the cumulative total duration of the follow-up in years across all subjects in the treatment group.

Additionally, the distribution of healthcare utilization related to major CIED infection within 12-months (or during the entire follow-up period) and related to major or minor CIED infection within 12-months (or during the follow-up period) will be compared between randomized treatment groups using negative binomial hurdle models for the following healthcare utilization parameters:

- Total days hospitalized for hospitalizations exceeding 24 hours
- Total outpatient visits where outpatient visits were defined as the sum of all hospitalizations less than 24 hours, emergency department visits, urgent clinic visits, and clinic visits.

Each negative binomial hurdle model will include the number of healthcare utilizations as the response, randomized treatment group as the independent predictor for both the zero distribution and negative binomial components of the model, and natural log of follow-up months as the offset. Under this parameterization, each hurdle model provides two estimates of the effect of the TYRX envelope on healthcare utilization: specifically (1) a measure of the change in the log odds of having at least one utilization in the TYRX group relative to the control group, and (2) a measure of the change in the intensity of healthcare utilization in the TYRX group relative to the control group. Exponentiated, the model estimates (1) and (2) can be interpreted as an odds ratio and conditional relative risk respectively.


The R package `psc1` will be used to fit each negative binomial hurdle model using the syntax below:

```
hurd.out <- hurdle(hcuParameter ~ trtgrp | trtgrp  
                  offset=logMonths,  
                  link="logit",  
                  dist="negbin")
```

where "hcuParameter" represents the count of the number health care utilization contacts for a subject, "trtgrp" is the randomized treatment group (parameterized as 1 = TYRX group, 0 = Control group), and "logMonths" is the natural log of the follow-up months. A link of "logit" requests that the logit link function be used for the zero component of the hurdle model, and a distribution of "negbin" requests that the negative binomial distribution be used to model the positive integer component of the hurdle model.

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 Amendment 2 to the WRAP-IT Statistical Analysis Plan	
<i>Clinical Investigation Plan Title</i>	<u>World-wide Randomized Antibiotic Envelope</u> <u>Infection Prevention Trial (WRAP-IT)</u>
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<i>Document Version</i>	Version 1.0
<i>Document Reference Number</i>	NA
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	<ul style="list-style-type: none">Initial Release	Alex Dedrick, Sr. Statistician

2. Introduction

2.1. Purpose

The purpose of this additional amendment to version 1.0 of the WRAP-IT Statistical Analysis Plan (SAP) is to document any modifications to the WRAP-IT SAP that were made following the interim analysis, but prior to breaking the blind for the final analysis. The primary purpose of this amendment is to further clarify specific sections in the WRAP-IT SAP. The remainder of WRAP-IT SAP version 1.0 and its amendment were unchanged.

3. Specific Changes

3.1. Definition of the Intent-To-Treat Cohort

3.1.1. Original Text from WRAP-IT SAP version 1.0 Amendment 1

Intention-to-Treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified. The ITT cohort will likely be the only cohort evaluated at the time of the interim analysis.

3.1.2. Rationale for Change

The original text in version 1.0 of the WRAP-IT SAP indicates subjects with complications post enrollment would be included for analysis. Subjects with complications after enrollment are defined as having an ongoing infection at procedure, receiving a heart transplant or a VAD, or receiving dialysis initiated after enrollment, but prior to procedure. These subjects are at a higher risk for infection and will be analyzed separately. A sensitivity analysis will be included to show differences between the ITT population and the cohort defined by these subjects.

3.1.3. Amended Text

Intention-to-Treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified. The ITT cohort will likely be the only cohort evaluated at the time of the interim analysis.

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modified Intent-to-Treat: The mITT cohort will exclude all enrolled subjects from the ITT cohort who, after enrollment become a higher risk for infection. This excludes subjects who meet any of the following criteria:

- Have an ongoing infection post-enrollment, but during procedure,
- Receive a heart transplant post-enrollment but prior to procedure,
- Receive a VAD (defined as LVAD, RVAD, or BiVAD) post-enrollment but prior to procedure,
- Initiate dialysis after enrollment but prior to procedure.

The mITT cohort will be used in a sensitivity analysis on the primary objective to show the effects of including subjects with a higher risk of infection and excluding them.

3.2. Determination of Subjects' Data for Analysis of Primary Objective #1

3.2.1. Original Text from WRAP-IT SAP version 1.0 Amendment 1

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope the AT or mAT cohorts as described above.

If the primary objective is not met for the ITT cohort, the analysis will be conducted for the AT/mAT cohorts.

3.2.2. Rationale for Change

The initial text did not take into consideration subjects who accumulate exclusion criteria after enrollment. An additional cohort is necessary to exclude subjects who are considered a higher risk for infection, and would have been excluded from the trial.

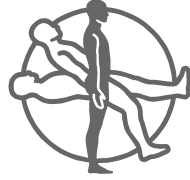
3.2.3. Amended Text

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope in the mITT, AT, or mAT cohorts as described above.

Sensitivity analyses will be performed for the mITT, AT, and mAT cohorts as necessary.

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**World-wide Randomized
Antibiotic Envelope
Infection Prevention Trial
(WRAP-IT)**

Statistical Analysis Plan

Version 1.0 + Amendments
Initial Version: July 21, 2015
Final Version: July 31, 2018

Pei Li, Sr Statistician
Kurt Stromberg, Sr Principal Statistician

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3.5 [REDACTED]	
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1 PURPOSE

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design of the WRAP-IT study, and the planned analyses that will be included in study reports. This SAP does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected.

2 RATIONALE FOR STUDY DESIGN

The World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) is a randomized, prospective, multi-center, single blinded, post-market, interventional clinical study. The study has three purposes. First, the WRAP-IT study will serve as a post-approval study for those geographies requiring a post-approval study to facilitate collection of complications related to the Cardiovascular Implantable Electronic Device (CIED) procedure or system in subjects randomized to receive the TYRX™ Absorbable Antibacterial Envelope (henceforth referred to as TYRX envelope). Next, this study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, or revision, or the implant of a de novo CRT-D. Subjects undergoing CIED generator replacement, upgrade, or revision or the implant of a de novo CRT-D system will be randomized to either receive the TYRX envelope or not to receive the TYRX envelope. Randomization will be 1:1 and be stratified by study site and device type, high power (ICD and CRT-D) vs. low power devices (IPG and CRT-P). Finally this large device study provides the unique opportunity to prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead. These features include the lead integrity alert (LIA), lead noise alert (LNA), RV pacing impedance, and high voltage (HV) pacing impedance to detect events that affect a RV lead's pacing, sensing, or defibrillation circuit lead system events (LSE).

The study is expected to be conducted at up to 225 sites worldwide with up to 7,764 subjects enrolled in order to randomize approximately 6,988 subjects. Enrollment of subjects receiving a replacement low power device (i.e. IPG or CRT-P) will be capped at approximately 25% of the total randomized study population (i.e. approximately 1,746 subjects). Relative to high power device recipients, patients receiving a low power device may be at reduced risk of a major CIED infection. Thus, to ensure an adequate CIED infection event rate in the control arm, there is a desire to include a higher proportion of high power devices in the trial.

The WRAP-IT study utilizes a group sequential design and has up to two planned analyses of the primary objective. The first analysis will occur when a minimum of 3,200 randomized subjects complete the 6-month visit and the final analysis will occur when all randomized subjects have the opportunity to complete the 12-month study visit. The study may be considered successful at the first analysis in which the primary objective is met. An independent Data Monitoring Committee (DMC) will periodically review the accumulating data and review the results of the analysis of the primary objective at each pre-specified analysis time point. Should the DMC indicate that the study is successful at the interim analysis, the study may continue to enroll and follow subjects to evaluate the effect of the TYRX envelope on CIED infections that develop post-12 months as well as collect additional follow-up in subjects with a defibrillation system in which to evaluate the lead monitoring features. However, subjects enrolled following review of the interim analysis may no longer be randomized upon recommendation of the DMC if the TYRX envelope is found to have a clear benefit.

The WRAP-IT Study Clinical Investigational Plan Version 1.0 was used to develop the SAP.

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Description of Baseline Variables

Standard baseline and relevant medical history will be collected on the eCRFs for all enrolled subjects. Baseline and medical history variables to be summarized include, but are not limited to: age, sex, race, device type (CRT-D, ICD, CRT-P, and IPG), number of previous CIED devices, NYHA class, arrhythmia history, and baseline medication use.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Baseline information will be summarized for all randomized subjects. The TYRX envelope and control groups will be compared using T-tests for continuous variables and the Chi-square test for categorical variables to quantify any imbalance in treatment groups.

3.1.2 Special Considerations

3.1.2.1 Pooling

The study may be conducted at up to 225 sites worldwide. Data from all centers that participate in this protocol will be combined for analysis. Expected participating geographies include, but are not limited to, the United States (US), Europe, the Middle East and Africa (EMEA), Greater China (Hong Kong), New Zealand, Latin America, the Association of South East Asian Nations (ASEAN) (Singapore and Malaysia), and India. However, since the majority of study centers will come from the US and the primary endpoint is likely to be rare, the primary objective results for US and outside the US (OUS) geographies will be presented and poolability analysis will be done. If a differential treatment effect ($P < 0.05$) is observed, we will investigate the cause of the differential treatment effect (e.g. by comparing baseline characteristics, procedure information and the medical practice etc).

3.1.2.2 Missing Data

If applicable, treatment of missing data is addressed within each objective.

3.1.2.3 Visit Windows

As the visit windows are meant as a guideline for centers, data from CRFs dated outside of the prescribed visit windows in the CIP will be used in all analyses.

3.1.2.4 Database Freeze

The visit cut-off date for the database freeze for the interim analysis will be the first date when a minimum of 3200 randomized subjects complete the 6-month visit. The visit cut-off date for the database freeze for the final analysis will be the date when all randomized subjects have had the opportunity to complete the 12-month study visit.

3.1.2.5 Randomization Date

There may be instances where the date and timestamp for the randomization process in the electronic database where randomization is performed may be after the date of the CIED procedure. This occurs when randomization is performed outside of the database (e.g. cases where Oracle Clinical is not accessible by the site) and the randomization

routine in the electronic database is executed to document the randomization process on a later date. For such cases, the randomization date will come from the randomization or implant procedure eCRF, whichever came first.

3.1.2.6 *Interim Analysis Type I Error Control*

The study has up to two planned analyses of the primary objective. The study may be considered successful at the first analysis in which the primary objective is met.

The first analysis will occur when approximately 50% of the total follow-up within 12-months of randomization occurs; based on enrollment projections described below this is defined as the point where 3200 randomized subjects complete the 6-month post-procedure visit. The purpose of this first analysis is two-fold:

1. To assess whether the study's primary objective has been met. If the DMC indicates that the study has met its objective, the study may continue to enroll and follow subjects to study the effect of the TYRX envelope on long-term CIED infections as well as accumulate LSEs. However, subjects enrolling following review of the interim analysis may no longer be randomized upon recommendation of the DMC if the TYRX envelope is found to have a clear benefit.
2. To assess whether the study may end earlier than planned for futility.

The timing of the interim analysis was selected so that sufficient data is collected to contribute to the interim analysis before decisions that impact the study are made. The Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) is used to control the overall alpha level at 5% (two-sided; 2.5% one-sided in the direction favorable to the TYRX envelope). This function spends the alpha at a level analogous to the O'Brien-Fleming boundary. The boundary condition at the interim analysis will be based on the information fraction at the interim analysis and computed by dividing the accrued number of major CIED infections observed at the interim analysis by the total number of major CIED infections anticipated at the final analysis.

To obtain the information fraction, a simulation will be performed to estimate the anticipated number of events pooled across both treatment groups which are expected to happen after the interim analysis. The event-free survival function is assumed to be piecewise exponential with two intervals (interval cutoff to be determined at interim analysis based on observed data). The hazard parameter in each interval will be estimated by data observed at interim analysis. Then complete follow-up data will be simulated to estimate of number of events by end of study. Sample R code for performing this simulation is found in section 4.2.

Assuming the information fraction at the interim analysis is 50%, the boundary condition at the interim analysis is 0.003 (2.75 on the Z-scale or 0.006 on the two-sided p-value scale) and is purposely low to allow early claims of study success only when the TYRX envelope is highly effective. At the final analysis, the boundary condition is 0.0238 (1.98 on the Z-scale or 0.0476 on the two-sided p-value scale) when the information fraction is 50% at the interim analysis. Since the analytical methods for the secondary objectives also utilize survival analysis methods, the same alpha spending function will be used to compute the success boundaries for the secondary objectives.

If the primary objective of the study is met, the secondary objectives will be tested using the Holm procedure to protect the overall type I error rate of the study and allow statistically valid claims of significance. Specifically, at analysis k ($k=1,2$), the ordered hypotheses $H_{(1k)}, H_{(2k)}, H_{(3k)}$ corresponding to the ordered p-values $p_{(1k)}, p_{(2k)}, p_{(3k)}$ of the secondary objectives will be tested based off the sequentially rejective algorithm. The hypothesis $H_{(1k)}$ is rejected if $p_{(1k)} \leq$

$\alpha_k/3$. Further, $H_{(jk)}$ is rejected at the j^{th} step if $p_{(jk)} \leq \alpha_k/(3 - j + 1)$. Otherwise, $H_{(jk)}, \dots, H_{(3k)}$ are retained and the algorithm terminates.

To help assess whether the study may end earlier than planned for futility, stochastic curtailment methods will be used to calculate the futility index for the primary objective. The futility index ($1 - P_1$, where P_1 is the predictive power observed at the interim analysis) is based on predictive power as computed as:

$$P_1 = \Phi \left\{ \frac{Z_1 \sqrt{I_2} - z_\alpha \sqrt{I_1}}{\sqrt{I_2 - I_1}} \right\}$$

where Z_1 is the test statistic at the interim analysis, I_1 is the information fraction at the interim analysis, I_2 is the information fraction at the final analysis (will be considered 1 at the interim analysis), and z_α is the critical value at the final analysis based on the alpha spending function. Although non-binding, a futility index greater than 0.9 at the interim analysis provides strong evidence that the study will not achieve its primary objective if the study were to continue to its full sample size and follow-up.

3.1.3 Early Study Success

Should the DMC indicate that the study is successful at the interim analysis, the study may continue to enroll and follow subjects to evaluate the effect of the TYRX envelope on CIED infections that develop post 12 months as well as collect additional follow-up in subjects with a defibrillation system in which to evaluate the lead monitoring features. If the study were to continue to enroll, it is anticipated that all subjects enrolled after the interim analysis would receive the TYRX envelope. Thus, for the final report, only those subjects randomized prior to the decision to end randomized allocation of the TYRX envelope would be included in the analysis of the primary and secondary objectives as well as ancillary objective #1.

3.1.4 Reports for which this Statistical Analysis Plan applies

This SAP applies to the interim analysis report and final report. However, the interim analysis report will likely evaluate the primary and secondary objectives as well as ancillary objective #1. This SAP also applies to the main study manuscript, though not everything specified here will be included in the manuscript.

3.1.5 Analysis Cohort

Intention-to-Treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified. The ITT cohort will likely be the only cohort evaluated at the time of the interim analysis.

As Treated (AT): The AT cohort includes subjects in the ITT cohort but will be defined using the treatment actually received at the time of their final index procedure. Randomized subjects without a procedure attempt and randomized subjects without a device remaining in the pocket at their final index procedure will be excluded from the AT cohort. Thus the number of subjects in the AT cohort will be less than the number of subjects in the ITT cohort. Furthermore, subjects with a device and with a TYRX envelope remaining in the device pocket following their procedure will be considered members of the TYRX group in the AT cohort regardless of randomization assignment. Similarly, subjects with a device, but without a TYRX envelope in their device pocket following procedure will be considered members of the control group in the AT cohort regardless of randomization assignment. For analyses stratified by device class (high power or low power) the analyses will stratify by the device class received at the index procedure implant unless the

device class is unknown (e.g., device not manufactured by Medtronic) in which case the device class as randomized will be used.

modified As Treated (mAT): The mAT cohort includes all subjects and follow-up time in the AT cohort that were successfully implanted with a CIED system (including the TYRX envelope if subject had a successfully placed TYRX envelope) up until the point where a CIED modification (i.e. system modification) occurred. Thus, subjects with a system modification for reasons other than device infection will be considered censored at the time of the system modification.

modified Intent-to-Treat: The mITT cohort will exclude all enrolled subjects from the ITT cohort who, after enrollment become a higher risk for infection. This excludes subjects who meet any of the following criteria:

- Have an ongoing infection post-enrollment, but during procedure,
- Receive a heart transplant post-enrollment but prior to procedure,
- Receive a VAD (defined as LVAD, RVAD, or BiVAD) post-enrollment but prior to procedure,
- Initiate dialysis after enrollment but prior to procedure.

The mITT cohort will be used in a sensitivity analysis on the primary objective to show the effects of including subjects with a higher risk of infection and excluding them.

3.2 Primary Objective

The primary study objective is to compare the rate of major CIED infections through 12-months post-procedure between the TYRX envelope group and the control group (no TYRX envelope).

3.2.1 Hypothesis

The primary study objective will be tested with the following hypothesis:

H₀: $\lambda_{T(t)} = \lambda_{C(t)}$ for all $t \leq 12$ months (365 days), versus

H_a: $\lambda_{T(t)} \neq \lambda_{C(t)}$ for some $t \leq 12$ months (365 days)

where $\lambda_{T(t)}$ is the hazard function for major CIED infection in the TYRX envelope group and $\lambda_{C(t)}$ is the hazard function for major CIED infection in the control group.

3.2.2 Endpoint Definition

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.

Major CIED infections are defined as CIED infections resulting in one or more of the following:

- CIED system removal
- Any invasive procedure (e.g. pocket opened) without system removal

- Treatment with antibiotic therapy if the subject is not a candidate for system removal and infection recurrence after completion of antibiotic therapy or evidence of deep infection with wound dehiscence, erosion, or purulent drainage.
- Death

3.2.3 Performance Requirements

If the hazard ratio : $\lambda_{T(t)} / \lambda_{C(t)}$ is significantly different from 1 (and less than 1), the major infection rate will be considered lower in the TYRX group.

3.2.4 Rationale for Performance Criteria

This study will evaluate the ability of the TYRX envelope to reduce major CIED infections through 12-months post-procedure following CIED generator replacement, upgrade, or revision, or the implant of a de novo CRT-D system. The hazard ratio is significantly different if the nominal p-value is less than the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function described above.

3.2.5 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the primary endpoint. The primary method to be used to test the primary objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) the subject is to receive as documented on the randomization eCRF and include treatment as an independent variable. This stratified Cox model assumes that the baseline hazard may be different for each device type, but that the underlying treatment effect is constant across device type. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if the subject was randomized but no procedure attempt) to: (1) onset date of a subject's first CIED infection meeting the primary endpoint, (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of last follow-up, or (5) 365 days post-procedure. However, if a subject has a major CIED infection during an unsuccessful procedure attempt; days of follow-up will be set to zero. Subjects not meeting the primary endpoint during the follow-up period will be considered censored at the end of their follow-up period as derived above. Based on this statistical test, it will be claimed that the TYRX envelope reduces major CIED infection if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function. Kaplan-Meier plots of freedom from major CIED infection will be presented by treatment group and by treatment group within each device type.

The following sample syntax in SAS will be used to evaluate the primary objective:

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt;
  strata device;
  *different baseline h0 but same HR across device**
run;
```

Sample R-code to fit the stratified Cox model is also displayed below:

```
coxph (Surv (survData$survDays, survData$survStatus) ~survData$trt +
strata (survDat$device))
```

If the primary objective is met at either the interim or final analysis time point, the following two assumptions will be tested:

1. Heterogeneity of the hazard ratio across device type:

The following sample syntax in SAS will be used to evaluate the homogeneity of treatment effect across device types for primary objective. If the interaction effect is significant at 0.05 level the treatment effect will not be assumed constant across device type and separate analyses will be performed for each device type.

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt device trt*device;
run;
```

2. Proportional hazards between treatment groups:

The proportional hazards assumption for the treatment effect will be examined graphically by examining plots of the complementary log-log CIED infection free time versus log time. Additionally, an interaction between event time and treatment group will be added to the model. If this interaction term is significant at the 0.05 level then this may provide evidence that the proportional hazards assumption is violated. Should the proportional hazards assumption be violated, inference regarding the effect of the TYRX envelope may be made at several different time points (e.g. 1-month, 6-months, and 12-months post-procedure). The following SAS code implements the test of the proportional hazards assumption:

```
*** PLOT THE COMPLEMENTARY LOG LOG;
proc lifetest data=<data> plot=(s, lls) noprint;
  time time*censor(0);
  strata trt;
  group device;
run;

*** TEST THE TIME VERSUS TREATMENT EFFECT;
proc phreg data=<data>;
  CLASS trt device;
  model eventtime*event(0)=trt trtTime;
  trtTime = trt*log(eventtime);
  strata device;
run;
```

3.2.6 Sample Size

Background

The reported prevalence rate of CIED infection varies widely in the literature and is dependent on the nature of data collection (retrospective vs prospective, single center vs multi-center), CIED infection definition, and population studied. The REPLACE study prospectively evaluated CIED infection requiring system removal or intravenous antibiotics in 1744 subjects undergoing a device replacement or upgrade. The infection rate at 6-months post-procedure for subjects receiving a device replacement was 1.4% and 1.1% for those subjects undergoing a device upgrade.

Analysis of 103,020 device implant claims from Medicare evaluated for Medtronic by Truven Analytics suggested that subsequent invasive procedures related to device infection occurred at a rate of 4.0% for CRT-D, 3.9% for ICDs, and 2.6% for pacemakers through 12-months. The 12-month CIED infection rate associated with replacement devices was 4.1% for CRT-D, 5.4% for ICDs, and 3.4% for pacemakers with 12-month infection rates associated with initial device implants ranging from 4.0% in CRT-Ds to 2.2% in pacemakers. However, examination of CIED infections reported in Medtronic studies, suggests that the Medicare claims data may overestimate the CIED infection rate that may be observed in clinical trials for initial implants by at least 50% (Table 1).

Table 1: 12-Month Infection Rates for Initial Implants by Device Type and Data Source

Device	Data Source	
	Medicare Claims Data 12-Month CIED Infection Rate	Medtronic Studies (12-month CIED Infection Rate (95% CI))
CRT-D	4.1%	2.0% (1.2% - 3.4%) ¹
ICD	3.0%	1.5% (0.3% - 6.7%) ²
Pacemaker	2.2%	1.2% (0.8% - 1.7%) ³

¹Based on 753 subjects with an attempted CRT-D implant in the REVERSE and BLOCK-HF studies.

²Based on 246 subjects from the Model 6947, 6948, and 6949 RV defibrillation lead studies

³Based on 2799 subjects from the 3830, 4074, 5076, Advisa MRI, EnRhythm, EnRhythm MRI, and SAVEPACe studies.

Based on the assumption that the Medicare claims data may overestimate the actual CIED infection rate that may be observed in a clinical trial, it is hypothesized that the 12-month infection rate for initial CRT-D implants, replacement (or upgrade) CRT-D implants, and replacement (or upgrade) ICD implants is 2.4% and is 0.6% for replacement pacemaker implants. Since low power replacement procedures (i.e. pacemaker and CRT-P replacement procedures) will be capped at 25% of the total sample size, an overall 12-month CIED infection rate for the control group is assumed to be 2% for sample size calculation purposes.

Retrospective evidence from the COMMAND study demonstrated that in 624 subjects consecutively implanted with the TYRX envelope the CIED infection rate was 0.48% and ranged from 0% during initial implant procedures to 1.05% during ICD/CRT-D replacement/revision procedures. Additionally, recently published data from Mittal, et. al showed that the CIED infection rate was 1.1% in 275 subjects that received the TYRX envelope compared to 3.6% in 275 propensity matched control subjects over a 6-month period across both low power and high power devices. Finally, early evidence from the CITADEL/CENTURION studies suggests that CIED infection rate among a cohort of 1000 ICD/CRT-D subjects receiving the TYRX envelope is 0.2% at 6-months post-replacement/upgrade; a 9-fold decrease compared to published controls at 6-months. Based on this experience, it is assumed that the TYRX envelope will reduce the risk of CIED infection by 50% through 12-months post-procedure.

Sample Size Calculation

The sample size is derived based on the following assumptions:

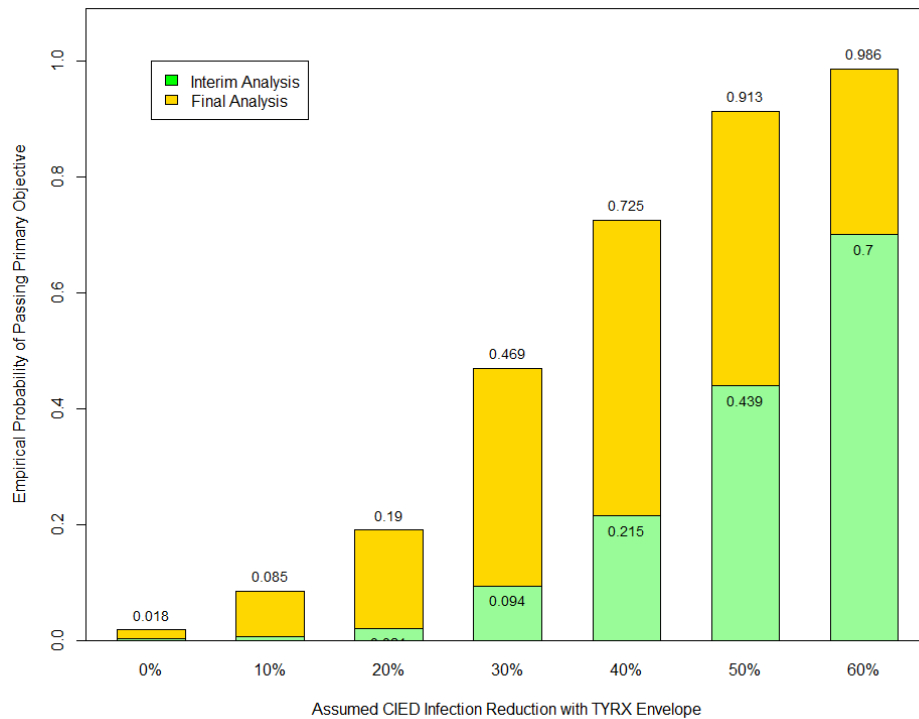
1. One-to-one randomization to the TYRX envelope or control group
2. Power to test the primary objective is at least 90%
3. One interim analysis and final analysis

4. The interim analysis will occur when approximately 50% of the statistical information has been accrued
5. One-sided alpha level of 2.5%
6. Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) which approximates O'Brien-Fleming boundaries
7. Assumed control CIED infection rate of 2% at 12-months
 - a. 2.4% for high power (CRT-D/ICD) devices
 - b. 0.6% for low power (pacemaker/CRT-P) devices
 - c. Low power devices are capped at 25% of the required sample size
8. TYRX envelope assumed to reduce the control infection rate by 50%
9. Non-binding futility assessment based on stochastic curtailment at the interim analysis
10. 15% annualized attrition rate that is independent of treatment group and infection status

The method of Lakatos (1988) as implemented in the POWER procedure of SAS v9.2, indicated 6,988 randomized subjects (3,494 randomized to each group) are required to test the primary objective based on the assumptions described above. Thus, up to 7,764 subjects may be enrolled to allow for up to a 10% discontinuation rate between enrollment (i.e. subject consent) and randomization.

A simulation study was performed to confirm the sample size calculation. In addition to the sample size assumptions described above, the simulation assumed that 50% of CIED infections occur within the first month of device procedure. Simulations were performed when the CIED infection risk reduction associated with the TYRX envelope ranged from 0% (null case) to 60%. Figure 1 confirms the sample size calculation and demonstrates that the type I error rate is well controlled. The program used to conduct the simulation analysis is found in section 4.1.

Figure 1: Empirical Power to Test the Primary Objective (n=6,988)



3.2.7 Determination of Subjects' Data for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle). Sensitivity analyses may be conducted by evaluating the performance of the TYRX envelope in the mITT, AT, or mAT cohorts as described above.

Sensitivity analyses will be performed for the mITT, AT, and mAT cohorts as necessary.

3.2.8 Missing Data

The primary analysis cohort will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. Since the primary statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a CIED infection meeting the primary endpoint. The log-rank test will be used to compare the study attrition rate for any reason (study exit or death) between randomized treatment groups to evaluate the pattern of data missingness by treatment group.

Additionally, as many cardiology journals are now requesting sensitivity analyses that include competing risk for death, a competing risks model will be used to test the effect of the TYRX envelope in the presence of competing risk of death unrelated to CIED infection should the study meet its primary objective. Sample R code for implementing the stratified competing risks model is as follows as recently described by Zhou et. al¹ is provided below:

R syntax below will be used to evaluate treatment effect on CIED infection with consideration of competing risk of death unrelated to CIED infection:

```
Library(crrSC)
Crrs(time, status, cov, strata, failcode=2, cencode=0)

# Status: 0 censor, 1 death unrelated to CIED infection, 2 CIED infection
# Cov: 0 control, 1 envelope
# Strata: low=1 high=2
```

3.2.9 Subgroup analysis

Subgroup analysis will be performed for subjects within high power (CRT-D, ICD) devices and patients with low power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g single chamber to dual chamber, or dual chamber to triple chamber, or low to high power) and patients without device upgrade will be analyzed separately. Additional subgroup analyses may also be performed on a post hoc basis.

The following sample syntax in SAS will be used for the subgroup analysis:

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt;
  by device;
run;
```

¹ B. Zhou, A. Latouche, V. Rocha, J. Fine. 2011. Competing risks regression for stratified data. *Biometrics* 67: 661-670.

Additionally, an interaction between the treatment group and subgroup will be added to the model to test for homogeneity of the treatment effect across subgroups. If this interaction term is significant at the 0.05 level the treatment effect will be considered heterogeneous between subgroups.

```
proc phreg data=<data>;  
    CLASS trt subGroup;  
    model eventtime*event(0)=trt subgroup trt*subGroup;  
run;
```

3.3 Secondary Objectives

The following secondary objectives will be evaluated to gain additional information about the safety and efficacy of the TYRX envelope in the study population. Provided the primary objective of the study is met with a statistically significant p-value, then the secondary objectives will be assessed. The Holm procedure will be used to control the family-wise type I error rate as described in section 3.1.2.6 in order to make statistically valid claims of significance.

3.3.1 Secondary Objective #1

Confirm that the TYRX envelope does not increase the CIED procedure-related or system-related complication rate through 12-months post-procedure.

3.3.1.1 Hypothesis

The first secondary objective will be tested with the following non-inferiority hypothesis:

H₀: $\lambda_T(t)/\lambda_C(t) \geq 1.33$ for $t \leq 12$ months (365 days), versus

H_a: $\lambda_T(t)/\lambda_C(t) < 1.33$ for $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for CIED system- or procedure-related complications in the TYRX envelope group and $\lambda_C(t)$ is the hazard function for CIED system-related complications in the control group. Rejecting the null hypothesis would indicate that the TYRX envelope does not increase the CIED system- or procedure-related complication rate by more than 33% on a relative scale or 4.4% on a linear scale when the underlying CIED system or procedure complication freedom rate at 12-months is 85%.

3.3.1.2 Endpoint

A CIED system-related complication is defined as an adverse event that meets the complication definition as determined by the CEC and is considered by the CEC to be related to one of the implanted CIED system components (i.e. device, RV lead, RA lead, LV lead, other lead, or the TYRX envelope).

A CIED procedure-related complication is defined as an adverse event that meets the complication definition as determined by the CEC and is considered by the CEC to be related to the CIED procedure (i.e. replacement/upgrade/new implant/revision) or a system modification including the TYRX envelope (if applicable).

3.3.1.3 Analysis Methods

All potential adverse events potentially related to the implanted system (i.e. device, leads), the TYRX envelope, or the CIED replacement/upgrade/implant or system modification procedure will be reported on the eCRFs as they occur. The CEC will adjudicate each reported adverse event for its relationship to the CIED system and CIED procedure. Additionally, the CEC will classify each CIED system-related or procedure-related adverse event as a complication or observation. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject was randomized but not implanted) to: (1) onset date of a subject's first CIED system related or procedure related complication (including the TYRX envelope where applicable), (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of last follow-up, or (5) 365 days post-procedure. Subjects with a procedure- and/or system-related complication occurring prior to their last CIED procedure attempt will their event date set to day zero. Subjects not having a CIED system-related or procedure-related complication during the follow-up period will be considered censored on the day as derived above.

The effect of the TYRX envelope on the rate of CIED system- or procedure-related complications will be tested using a Cox proportional hazards regression model stratified by device type (low power versus high power) containing an indicator term for treatment group. The observed hazard ratio from the Cox model will be compared to the non-inferiority margin of 1.33. The null hypothesis will be rejected in favor of the alternative and the TYRX envelope will be considered non-inferior to the control group if the p-value computed from the non-inferiority test is less than the type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons. Kaplan-Meier plots of freedom from system- or procedure-related complications will be presented by treatment group and by treatment group within each device type.

The following sample syntax in SAS will be used to evaluate the second objective #1:

```
proc phreg;
  class trt device;
  model eventtime*event(0)=trt;
  estimate trt 1/testvalue=0.285 lower; **ln(1.33)=0.285**
  strata device;
run;
```

If secondary objective #1 is met at either the interim or final analysis time point, the following two assumptions will be tested in an analogous fashion as described for the primary objective:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.3.1.4 Power to test the objective

Background

Table 2 displays the procedure- or system-related complication rates from several Medtronic and non-Medtronic sponsored studies. These data indicate that complications related to the implanted system (i.e. device and leads) or procedure range from 4.0% to

24.7% depending on complication definition, devices studied, and study population. Based on these data it appears reasonable based on the mix of devices and population under investigation in the WRAP-IT study that the underlying system or procedure complication free rate could range from 80% to 90% at 12-months post-procedure.

Table 2: System or Procedure-Related Complications Reported Previous Studies

Study	Devices Studied	Population	Time Frame	Complication Rate (95% CI)
Gould et. al 2008 ¹	ICD (n=451)	Replacements	12-months	9.1% (NR)
REPLACE ²	IPG (n=515) ICD (n=327) CRT-D (n=175) CRT-P (n=14)	Replacements	6-months	4.0% (2.9%-5.4%)
REPLACE	IPG (n=329) ICD (n=320) CRT-D (n=49) CRT-P (n=15)	Upgrades	6-months	15.3% (12.7% - 18.1%)
BLOCK-HF	CRT-D (n=230)	New Implants	12-months	22.9% (18.0% - 29.0%)
BLOCK-HF	CRT-P (n=531)	New Implants	12-months	17.7% (14.7% - 21.3%)
REVERSE	CRT-D (n=523)	New Implants	12-months	17.0% (14.0% - 20.5%)
REVERSE	CRT-P (n=104)	New Implants	12-months	24.7% (17.5% - 34.4%)
4074 Study	IPG (n=132)	New Implants	6-months	13.9% (9.0% - 21.1%)
EnRhythm MRI ³	IPG (n=469)	New Implants	12-months	11.3% (8.8% - 14.6%)
Advisa MRI ³	IPG (n=269)	New Implants	6-months	9.2% (6.3% - 13.4%)

¹Gould et. al. 2008. Heart Rhythm 5: 1675-1681. Major complication defined as post-operative death, nonfatal MI, cardiogenic shock, or event requiring reoperation.

²Poole et. al. 2010. Circulation 122:1553-1561. Major complications defined as an event defined in Table 1 of the manuscript. In general major complications required invasive intervention.

³Does not include system complications related to the RA lead only.

Power Calculation

Since the primary objective of the study dictates the sample size for the study, the power to test this secondary objective under several scenarios was determined based on the method of Lakatos as implemented in PASS 2008. The following assumptions were made in the power calculation:

1. Sample size of 6,988 subjects randomized 1:1 to the TYRX envelope or control group
2. One interim analysis and final analysis
3. The interim analysis will occur when approximately 50% of the follow-up is accrued
4. One-sided alpha level of 2.5%
5. Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative 4 (-4) which approximates O'Brien-Fleming boundaries and means the final test will be conducted at a one-sided alpha-level of 0.0238 which is analogous to a two-sided alpha level of 0.0476.
6. 15% annualized attrition rate that is independent of treatment group and system-related complication
7. 12-month system- or procedure-related complication rate in the control group could range from 10% to 20%
8. The TYRX envelope has no effect on the system- or procedure-related complication rate

9. Non-inferiority margin of 33% on a relative scale or 4.4% on a linear scale when the underlying CIED system complication freedom rate at 12-months is 85%

Table 3 indicates that the statistical power to test the non-inferiority hypothesis associated with secondary objective #1 is greater than 94% based on the assumptions above across a range of plausible control group event rates.

Table 3: Power to Test Secondary Objective #1 with Sample Size of 6,988 Subjects

12-month system-related Complication Free Rate	Control Group Hazard Rate	Non-inferiority Margin (Relative Scale)	Non-inferiority Margin (Linear Scale) ¹	Power
90%	0.1054	1.33	3.1%	94.9%
88%	0.1278		3.6%	97.6%
86%	0.1508		4.2%	98.9%
85%	0.1625		4.4%	99.3%
84%	0.1744		4.7%	99.5%
82%	0.1985		5.2%	99.8%
80%	0.2231		5.7%	99.9%

¹The non-inferiority margin on the linear scale is defined as the difference in the survival curves for the event rate at 12-months post-randomization between the control group and the TYRX™ Absorbable Antibacterial Envelope group.

3.3.1.5 Determination of Subjects' Data for Analysis

Since non-inferiority tests based on intention-to-treat principles may be anti-conservative, the results of the non-inferiority test will be reported for both the ITT and AT cohorts as recently suggested². However, statistical inference for this objective will be based on the AT cohort. All randomized subjects and all follow-up from randomized subjects is included in the ITT cohort regardless of treatment received. For the AT cohort, all follow-up from all subjects will be included, but the analysis will be based on the treatment the subject actually received at the time of their original CIED procedure.

3.3.1.6 Missing Data

The analysis cohorts will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. Since the statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a CIED system- or procedure-related complication. As described in section 0 the log-rank test will be used to compare the study attrition rate for any reason between randomized treatment groups to evaluate the pattern of data missingness.

3.3.1.7 Subgroup Analyses

Subgroup analysis will be performed for subjects within high power (CRT-D, ICD) devices and patients with low power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g single chamber to dual chamber, or dual chamber to triple chamber, or lower to high power) and patients without device upgrade will be analyzed separately using the methods described in section 3.2.9.

² Head, SJ et al. 2012. Non-inferiority study designs: lessons to be learned from cardiovascular trials. *European Heart Journal* 33(11): 1318-1325.

3.3.2 Secondary Objective #2

Compare the major CIED infection rate during the entire follow-up between the TYRX envelope group and the control group.

3.3.2.1 Hypothesis

The second secondary objective will be tested with the following hypothesis:

H₀: $\lambda_T(t) = \lambda_c(t)$ for all $t \leq T$, versus

H_a: $\lambda_T(t) \neq \lambda_c(t)$ for some $t \leq T$

where $\lambda_T(t)$ is the hazard function for major CIED infection in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for major CIED infection in the control group during the entire follow-up period.

3.3.2.2 Endpoint Definition

Major CIED infection is defined in section 3.2.2.

3.3.2.3 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the major CIED infection definition. The primary method to be used to test this objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject was randomized but not implanted) to: (1) onset date of a subject's first CIED infection meeting the primary endpoint, (2) study exit date (if exited), (3) date of death (if death occurs), or, (5) date of last follow-up. Subjects who meet the endpoint prior to their last CIED procedure attempt will be considered to have met the endpoint on day zero. Subjects not having a major CIED infection during the follow-up period will be considered censored at their last follow-up day. Based on this statistical test, it will be claimed that the TYRX envelope reduces major CIED infection during the entire study period if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons. Kaplan-Meier plots of freedom from major CIED infection will be presented by treatment group and by treatment group within each device type.

The SAS code for implementing the stratified Cox regression model will be similar to the sample code described in 3.2.5.

If secondary objective #2 is met at either the interim or final analysis time point, the following two assumptions will be tested as described above:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.3.2.4 Determination of Subjects' Data for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

If the objective is not met for the ITT cohort, the analysis will be conducted for the AT/mAT cohorts.

3.3.2.5 Missing Data

The primary analysis cohort for this objective will include all follow-up from all randomized subjects through the end of the study or visit cutoff for the interim analysis (i.e. Intention-to-Treat principle). Since the statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the end of the study (or visit cutoff) without experiencing a major CIED infection. The log-rank test will be used to compare the study attrition rate for any reason (study exit or death) between randomized treatment groups to evaluate the pattern of data missingness by treatment group.

Additionally, a competing risks model will be used to test the effect of the TYRX envelope in the presence of the competing risk of death unrelated to CIED infection should this objective be met as described in section 0.

3.3.2.6 Subgroup Analyses

Subgroup analysis will be performed for subjects within high power (CRT-D, ICD) devices and patients with low power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g single chamber to dual chamber, or dual chamber to triple chamber, or low to high power) and subjects without device upgrade will be analyzed separately using the methods described in section 3.2.9.

3.3.3 Secondary Objective #3

Compare the rate of major and minor CIED infections through 12-months post-procedure between the TYRX envelope group and the control group.

3.3.3.1 Hypothesis

The third secondary objective will be tested with the following hypothesis:

H₀: $\lambda_T(t) = \lambda_C(t)$ for all $t \leq 12$ months (365 days), versus

H_a: $\lambda_T(t) \neq \lambda_C(t)$ for some $t \leq 12$ months (365 days)

where $\lambda_T(t)$ is the hazard function for major and minor CIED infection in the TYRX envelope group and $\lambda_C(t)$ is the hazard function for major and minor CIED infection in the control group.

3.3.3.2 Endpoint Definition

CIED infections, including major CIED infections are defined in section 3.2.2. Minor CIED infections are CIED infections that are not classified as major CIED infections.

3.3.3.3 Analysis Methods

All potential CIED infections will be collected on the eCRFs as they occur. The CEC will adjudicate each potential CIED infection for its relationship to the CIED and determine whether it meets the major CIED infection definition. Those infections related to the CIED that do not meet the major CIED infection will be considered minor CIED infections. The primary method to be used to test this objective will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject is randomized but not implanted) to: (1) onset date of a subject's first major or minor CIED infection, (2) study exit date (if exited), (3) date of death (if death occurs), (4) date of last follow-up, or (5) 365 days post-procedure. Subjects who meet the endpoint prior to their last CIED procedure attempt will be considered to have met the endpoint on day zero. Subjects not having a major or minor CIED infection during the follow-up period will be considered censored on the day as derived above. Based on this statistical test, it will be claimed that the TYRX envelope reduces major or minor CIED infection if the hazard ratio estimate is less than one and the resulting p-value from the Wald test falls below the specified type I error boundary as determined by the Hwang-Shih-DeCani alpha spending function and Holm adjustment for multiple comparisons. Kaplan-Meier plots of freedom from major or minor CIED infection will be presented by treatment group and by treatment group within each device type.

The SAS code for implementing the stratified Cox regression model will be similar to the sample code described in 3.2.5.

If secondary objective #3 is met at either the interim or final analysis time point, the following two assumptions will be tested as described above:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.3.3.4 Determination of Subjects' Data for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

If the objective is not met for the ITT cohort, the analysis will be conducted for the AT/mAT cohorts.

3.3.3.5 Missing Data

The primary analysis cohort for this objective will include all follow-up from all randomized subjects through the 12-month visit or 365 days post-randomization, whichever occurs first. Since the statistical methods involve survival methods all follow-up from all randomized subjects will be included. However, missing data could arise if a randomized subject exits the study or dies prior to the 12-month visit without experiencing a major or minor CIED infection. The log-rank test will be used to compare the study attrition rate for any reason

(study exit or death) between randomized treatment groups to evaluate the pattern of data missingness by treatment group.

Additionally, a competing risks model will be used to test the effect of the TYRX envelope in the presence of the competing risk of death unrelated to CIED infection should this objective be met as described in section 0.

3.3.3.6 Subgroup Analyses

Subgroup analysis will be performed for subjects within high-power (CRT-D, ICD) devices and subjects with low-power (pacemaker, CRT-P) devices to assess the performance of the TYRX envelope within each of these device types. In addition, subgroups of subjects with device upgrade (e.g. single chamber to dual chamber, or dual chamber to triple chamber, or low to high power) and subjects without device upgrade will be analyzed separately using the methods described in section 3.2.9.

3.4 Ancillary Objectives

The following ancillary objectives are intended to gain additional information about the performance of the TYRX envelope. The type I error rate is not controlled for the ancillary objectives. Not all ancillary objectives may be evaluated if the study's primary objective is not met.

3.4.1 Ancillary Objective #1: Mortality

To compare all-cause mortality rates between the TYRX envelop group and the control group.

3.4.1.1 Endpoint

Death for any cause

3.4.1.2 Hypothesis

This ancillary objective will be tested with the following hypothesis:

H₀: $\lambda_T(t) = \lambda_c(t)$ for all $t \leq T$, versus

H_a: $\lambda_T(t) \neq \lambda_c(t)$ for some $t \leq T$

where $\lambda_T(t)$ is the hazard function for death for any cause in the TYRX envelope group and $\lambda_c(t)$ is the hazard function for death any cause in the control group during the entire follow-up period.

3.4.1.3 Analysis Methods

The primary method to be used to evaluate the hypothesis above will be the Cox proportional hazard model. The Cox model will be stratified by device type (low power versus high power) and include treatment as an independent variable. Days of follow-up for each subject will be set to the minimum of days from last procedure attempt (or randomization if a subject was randomized but not implanted) to the (1) date of death or (2) last study contact date. Subjects alive at their last follow-up day will be censored on their last day as derived above. A p-value less than 0.05 will be considered statistically

significant. Kaplan-Meier plots of subject survival will be presented by treatment group and by treatment group within each device type.

The SAS code for implementing the stratified Cox regression model will be similar to the sample code described in 3.2.5

If ancillary objective #1 is met at either the interim or final analysis time point, the following two assumptions will be tested as described above:

1. Heterogeneity of the hazard ratio across device type
2. Proportional hazards between treatment groups

3.4.1.4 Determination of Subjects for Analysis

All randomized subjects will be included in the primary analysis regardless of the treatment they actually receive or their study compliance (i.e. Intention-to-Treat principle).

If the objective is not met for the ITT cohort, the analysis will be conducted for the AT cohort.

3.4.2 Ancillary Objective #2: CIED procedure success rate

Evaluate the CIED procedure success rate in the TYRX envelope group and the control group

3.4.2.1 Analysis Methods

Information related to the CIED procedure (i.e., initial implant or index replacement/upgrade or index system revision) will be collected on the procedure eCRF. A procedure attempt is defined as any CIED procedure where the device pocket is opened or venous access was gained (i.e., skin was cut). A successful procedure is defined as an implant attempt where the device is successfully connected to the system's leads and the CIED system remains in the body and the device pocket is closed. Additionally, for those subjects randomized to the TYRX envelope group, the TYRX envelope must also remain in the device pocket following pocket closure to qualify as a successful CIED procedure.

Specifically, for all subjects with a procedure attempt, a CIED procedure can only be considered successful if the question on the procedure CRF "Was a generator in the pocket following the procedure?" is answered as "Yes". Additionally, for those subjects randomized to the TYRX envelope group and with an attempted implant of the TYRX envelope, the question "Was the TYRX envelope in the device pocket following the implant procedure?" must also be answered as "Yes". Note that for purposes of determining procedure success, subjects with a CRT device where the LV lead cannot be placed adequately may still be considered a success if the generator remains in the pocket. In these cases, a system modification form would be required if another LV lead implant attempt is made during a separate procedure.

The CIED procedure success rate will be defined on a per subject basis as the number of subjects with their last CIED procedure considered successful divided by the number of subjects with at least one CIED procedure attempt. Fisher's exact test will be used to compare the procedure success rate between the TYRX envelope group and the control group.

The following sample syntax in SAS will be used to evaluate the ancillary objective #2:

```
proc freq;
  tables trt*success /exact cmh;
  weight count;
run;
```

Fisher's exact test will also be used to compare the percentage of subjects with more than one procedure attempt (i.e. more than one CIED procedure CRF) by randomized treatment group. For each randomized treatment group the denominator will be the number of subjects with a successful procedure and the numerator will be the number of subjects with a successful procedure requiring more than one procedure to obtain the successful procedure.

3.4.2.2 *Determination of Data for Analysis*

The primary analysis cohort will be the ITT population with the following additional requirements:

1. A subject must have a CIED procedure attempt (e.g., skin cut)
2. Subjects randomized to the TYRX group must have had an attempt to implant the TYRX envelope. Specifically, subjects who crossed over to the control group without an attempted TYRX envelope implant were excluded from this analysis. For example, this includes subjects who were crossed over due to TYRX inventory issues or site error.
3. Subjects randomized to the control group that crossed over to the TYRX envelope group during their implant attempt will be conservatively excluded from the analysis cohort for this objective since it is not possible to accurately determine the number of control group subjects with an attempted crossover to the TYRX envelope group where the TYRX envelope was not successfully implanted.

3.4.3 Ancillary Objective #3: Summarize adverse events

To summarize adverse events by treatment group

3.4.3.1 *Analysis Methods*

Subjects will be queried for AEs at all scheduled and unscheduled visits. All AEs potentially related to the CIED system, CIED implant or system modification procedure, and all SAEs regardless of their relationship to the CIED system or CIED procedure (including the TYRX envelope if applicable) will be collected. Medtronic safety specialists will ensure that at a minimum all AEs that are potentially related to the CIED system (including the TYRX envelope), or CIED procedure, or death are classified by the CEC. Summary tables will be compiled categorizing the AEs with respect to procedure relatedness, CIED relatedness (including CIED component), and TYRX envelope relatedness. For events classified by the CEC, the CEC classification will be used in the analysis. In cases where only the investigator classifies the event, the investigator's classification will be used. In addition, the number of events and number of subjects with events by MedDRA term will be displayed. Additionally, the nominal p-value from the log-rank test will be used to identify system- or procedure-related AEs occurring on or after a CIED procedure attempt by MedDRA preferred term that may differ between treatment groups. This test does not protect the type I error, but may help identify specific AEs that differ between randomized treatment group for further evaluation. These tests will only be performed for preferred terms that occur in more than five subjects.

3.4.3.2 Determination of Data for Analysis

All adverse events collected during the study will be included in this analysis.

3.4.4 Ancillary Objective #4: Predictors of CIED infection

To identify predictors of major CIED infection

3.4.4.1 Analysis Methods

Subject demographics and medical history including previous device history will be collected at baseline. CIED procedure-related variables such as antibiotic prophylaxis, surgical site preparation, procedure duration, device type, and number of leads will be collected for each CIED procedure. Additionally, device characteristics such as impedance, optivol fluid status, and heart rate variability etc. will be collected via device interrogations at each follow-up visit. Cox regression models will be employed using subjects in the control group to identify factors that may be associated with major CIED infection. Additionally, multivariable Cox models may be used to develop a risk model for major CIED infection. For any such multivariable Cox model, the number of degrees of freedom available and hence the number of candidate predictors available (and their functional form) for modelling will be determined by the number of major CIED infections in the control group. This analysis will be exploratory in nature.

3.4.4.2 Determination of Data for Analysis

All subjects randomized to the control group with a CIED procedure attempt who do not receive the TYRX envelope during their CIED procedure.

3.4.5 Ancillary Objective #5: Quality of Life

Summarize quality of life.

3.4.5.1 Analysis Methods

Subjects will be asked to complete the EQ-5D questionnaires at baseline and at the 12-month visit (or study exit if the subject exits the study for reasons other than lost to follow-up prior to completing the 12-month visit). Additionally, subjects with a CIED infection will be asked to complete the EQ-5D within two weeks following their CIED infection diagnosis and at 1-month, 3-months, and 6-months post-CIED infection diagnosis.

The EQ-5D summary health score is calculated based on five “dimension” questions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For subjects completing the EQ-5D-3L questionnaire (primarily OUS subjects) each dimension has three options, which are in general: 1=no problem, 2=some problem, 3=extreme problem. For subjects completing the EQ-5D-5L questionnaire (primarily US subjects) each dimension has five options which are in general: 1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, 5=unable to perform.

For purposes of the final study report, EQ-5D summary scores will be standardized to the EQ-5D-3L summary health score using EQ-5D-5L to EQ-5D-3L crosswalk value set current at the time the final report is prepared, unless EQ-5D-5L value sets become available from EuroQoL during the WRAP-IT study for geographies using the EQ-5D-5L.

Each subject's summary health score will be standardized to the same country value set (e.g. US) regardless of the subject's origin using the appropriate EQ-5D-3L value set.

Medtronic's healthcare economics group may request additional summaries of the EQ-5D data following study completion for conducting cost effectiveness analyses described in the healthcare economics analysis plan.

Descriptive statistics will be used to summarize the change in EQ-5D scores from baseline to the 12-month visit by infection status. Additionally, the changes in EQ-5D between CIED infection and post-CIED infection will be computed using summary statistics for all subjects with a major CIED infection as classified by the CEC. More detailed analysis methods will be described in the health economics Statistical Analysis Plan.

Bar charts will be used to present results from the EQ-5D descriptive system as a health profile. Summary health score will be presented in tables similar to shown below:

EQ-5D		Baseline				12-months				Change		
		N	Mean ± Std.	Median	Range	N	Mean ± Std.	Median	Range	N	Mean ± Std.	95% CI
EQ-5D Health Score	Infection											
	No Infection											
EQ-5D Visual Analog Scale	Infection											
	No Infection											

3.4.5.2 Determination of Data for Analysis

Completed EQ-5D questionnaires from all randomized subjects will be used to describe the changes in EQ-5D score from baseline. All completed EQ-5D questionnaires following an adjudicated CIED infection will be used to summarize the change in EQ-5D score from baseline following CIED infection.

3.4.6 Ancillary Objective #6: Healthcare System Cost Effectiveness

Objective

To assess the cost-effectiveness of the TYRX envelope.

Analysis Methods

Health care utilizations (HCUs) related to suspected CIED infection will be collected on the eCRFs. HCUs related to CIED infection include all hospitalizations, emergency department visits, urgent care, or unscheduled follow-up visits associated with the suspected CIED infection regardless of location of care.

For each major CIED infection as classified by the CEC, the following information will be compiled and provided to Medtronic's healthcare economics group:

- Subject identifier, randomized treatment group, and treatment actually received
- For each inpatient hospitalization the hospitalization admission date, discharge date, total hours in ICU, and total hours in cardiac ward

- For each outpatient visit the type of outpatient visit, provider type, and visit date
- Date and type of any long-term health care facility stay
- Start date, stop date, frequency per week, and frequency per day for each session of home health care
- Medications used to treat the CIED infection as recorded on the AE eCRF associated with the major CIED infection

Medtronic's healthcare economics group (or their designees) will use this information to evaluate the cost-effectiveness of the TYRX envelope and develop subsequent ancillary study publications. The methodology for the cost-effectiveness models is detailed in the WRAP-IT health economics analysis plan.

For purposes of the final report, the following healthcare utilization parameters will be summarized by randomized treatment group for subjects with a major CIED infection within 12-months, major CIED infection during the entire follow-up period, any major or minor CIED infection within 12-months, and any major or minor CIED infection during the entire follow-up period:

- Total days hospitalized for hospitalizations exceeding 24 hours
- Days in intensive care unit (24 hours = 1 day and fractional days rounded up)
- Days in cardiac ward (24 hours = 1 day and fractional days rounded up)
- Total days hospitalized for hospitalization less than 24 hours
- Number of emergency department visits
- Number of urgent clinic visits
- Number of clinic visits

For each healthcare utilization parameter, the rate of healthcare contacts per year (e.g., hospitalized days per year, number of emergency department visits) in each randomized treatment group will be computed by dividing the total number of contacts by the cumulative total duration of the follow-up in years across all subjects in the treatment group.

Additionally, the distribution of healthcare utilization related to major CIED infection within 12-months (or during the entire follow-up period) and related to major or minor CIED infection within 12-months (or during the follow-up period) will be compared between randomized treatment groups using negative binomial hurdle models for the following healthcare utilization parameters:

- Total days hospitalized for hospitalizations exceeding 24 hours
- Total outpatient visits where outpatient visits were defined as the sum of all hospitalizations less than 24 hours, emergency department visits, urgent clinic visits, and clinic visits.

Each negative binomial hurdle model will include the number of healthcare utilizations as the response, randomized treatment group as the independent predictor for both the zero distribution and negative binomial components of the model, and natural log of follow-up months as the offset. Under this parameterization, each hurdle model provides two estimates of the effect of the TYRX envelope on healthcare utilization: specifically (1) a measure of the change in the log odds of having at least one utilization in the TYRX group relative to the control group, and (2) a measure of the change in the intensity of healthcare utilization in the TYRX group relative to the control group. Exponentiated, the model estimates (1) and (2) can be interpreted as an odds ratio and conditional relative risk respectively.

The R package `pscl` will be used to fit each negative binomial hurdle model using the syntax below:

```
hurd.out <- hurdle(hcuParameter ~ trtgrp | trtgrp
                  offset=logMonths,
                  link="logit",
                  dist="negbin")
```

where "hcuParameter" represents the count of the number health care utilization contacts for a subject, "trtgrp" is the randomized treatment group (parameterized as 1 = TYRX group, 0 = Control group), and "logMons" is the natural log of the follow-up months. A link of "logit" requests that the logit link function be used for the zero component of the hurdle model, and a distribution of "negbin" requests that the negative binomial distribution be used to model the positive integer component of the hurdle model.

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SAS syntax for this analysis will be similar to below:

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4 APPENDIX

4.1 Sample Size Simulation Program

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4.3 Change History

Table 4: Change History

Applicable Sections	Change	Rationale
Amendment 1 – 08JAN2018		
Section 3.1.5	Modified the definition of As Treated cohort	The original text in version 1.0 of the WRAP-IT SAP was unclear as to whether subjects without a procedure attempt or with no successful procedure attempts would be included in the AT cohort. Additionally, the original text did not indicate whether the analysis of the AT cohort would stratify by the device type (high power or low power) as randomized or by the device type as actually implanted.
Section 3.4.2.1	Modified the definition of Analysis Cohort for Ancillary Objective #2 (CIED Procedure Success)	The DMC informed Medtronic on 25 February 2017 that Medtronic may want to consider revising the analysis cohort for the analysis of the procedure success rate (ancillary objective #2), as several subjects randomized to the TYRX envelope group never had a TYRX envelope implant attempt. Reasons for not having a TYRX envelope implant attempt included “TYRX envelope inventory issues” and “study site error”.
Section 3.4.2.2	Modified the determination of Subjects for Analysis for Ancillary Objective #2 (CIED Procedure Success)	
Section 3.4.6	Analysis Methods for Ancillary Objective #6: (Healthcare System Cost Effectiveness)	There were two reasons for modifying the original text in version 1.0 of the WRAP-IT SAP. First, the blinded study statistician noticed that the distribution of healthcare utilization parameters had many more zeros (i.e., subjects with value of zero for healthcare utilization parameter) than could be accommodated by a negative binomial distribution. Specifically, the distribution of these variables was highly zero inflated. Thus, it was necessary to change from the originally specified negative binomial model to a negative binomial hurdle model to account for the zero inflation. Secondly, the healthcare cost effectiveness analyses are being specified in the healthcare economics analysis plan. Moreover, since many of the healthcare cost effectiveness analyses will likely occur following distribution of the WRAP-IT final clinical study report, it was necessary to identify which healthcare utilization analyses would appear in the final report.
Amendment 2 – 31JUL2018		
Section 3.1.5	Added the modified Intent-to-Treat cohort definition	The original text in version 1.0 of the WRAP-IT SAP indicates subjects with complications post enrollment would be included for analysis. Subjects with complications after enrollment are defined as having an ongoing infection at procedure, receiving a heart transplant or a VAD, or receiving dialysis initiated after enrollment, but prior to procedure. These subjects are at a higher risk for infection and will be analyzed separately. A sensitivity analysis will be included to show differences between the ITT population and the cohort defined by these subjects.

Section 3.2.7	Added the modified intent-to-treat to the list of cohorts to be analyzed if the primary objective is not met	The initial text did not take into consideration subjects who accumulate exclusion criteria after enrollment. An additional cohort is necessary to exclude subjects who are considered a higher risk for infection, and would have been excluded from the trial.
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