

WRAP-IT STUDY WITH THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE

The **World-wide Randomized Antibiotic Envelope Infection Prevention Clinical (WRAP-IT) Study** is the first large-scale study of its kind to evaluate an antibacterial envelope in CIED patients who are at risk for infections.

BACKGROUND

The WRAP-IT Study is a Cardiovascular Implantable Electronic Device (CIED) replacement complication study targeted at the 2 largest complications related to CIED implants: infection and lead system events. Medtronic will utilize the TYRX Absorbable Antibacterial Envelope and its proprietary Lead Monitoring Algorithms in an attempt to drive down the rate of these complications, which could potentially result in better patient outcomes and substantial cost savings to the healthcare system.

PURPOSE

- Evaluate the ability of the TYRX Absorbable Antibacterial Envelope to help reduce major CIED infections through 12 months post-implantation
- Serve as a post-approval registry for those geographies requiring post-marketing data on mechanical complications, such as generator migration, related to the CIED implant procedure or system
- Prospectively characterize the performance of Medtronic's lead monitoring features in subjects whose CIED system includes a transvenous RV defibrillation lead

DESIGN

TYRX Absorbable Antibacterial Envelope Prospective, Randomized, Single-Blind, International Post-Market, Multi-Center Study

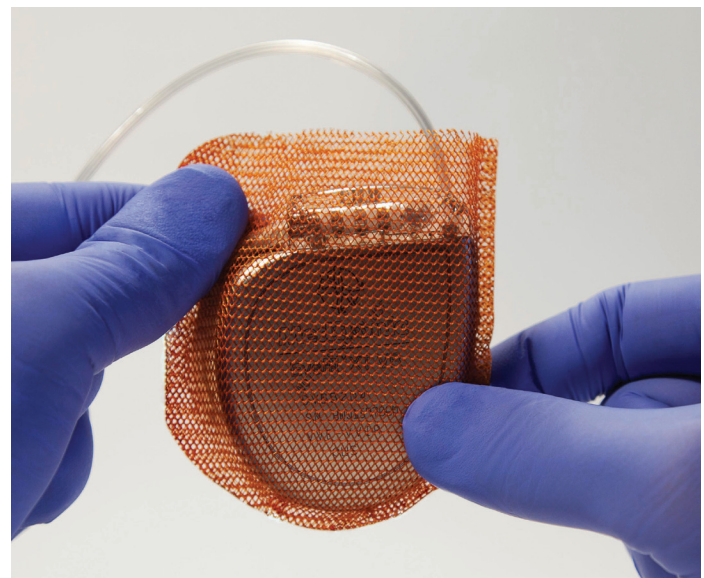
- Up to 225 investigational sites projected worldwide (including the United States, Europe, Middle East, Greater China, New Zealand, Latin America, Singapore, Malaysia, India)
- Up to 7,764 subjects projected for enrollment
- Medtronic-only generators (including upgrades, replacements, and revisions)

The anticipated study duration is approximately 36 months. Subjects will be followed for a minimum of 12 months, and may be followed for the full 36 months, depending on when they enroll in the study.

The study will also prospectively evaluate the performance of Medtronic lead monitoring algorithms – such as Lead Integrity Alert (LIA) and Lead Noise Alert (LNA) software – to identify lead system issues in defibrillator patients.

METHODOLOGY

- 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 Absorbable Antibacterial Envelope or not to receive the TYRX Absorbable Antibacterial Envelope.
- Randomization will be 1:1 and stratified by study site and device type: high power (ICD and CRT-D) vs. low power devices (IPG and CRT-P).
- The rate of major infection in CIED patients at 12 months following a procedure, and the consequent healthcare costs, will be compared between patients receiving a TYRX Absorbable Antibacterial Envelope at implantation and those not receiving the Envelope.



OBJECTIVES

Primary Objective:

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

Secondary Objectives:

- Confirm that the TYRX Absorbable Antibacterial Envelope does not increase the CIED procedure-related or system-related mechanical complication rate through 12 months post-procedure
- Compare the major CIED Infection rate during the entire follow-up between the TYRX Absorbable Antibacterial Envelope group and the control group
- Compare the rate of major and minor CIED Infections through 12 months post-procedure between the TYRX Absorbable Antibacterial Envelope group and the control group

Post-Market CE Mark Objective:

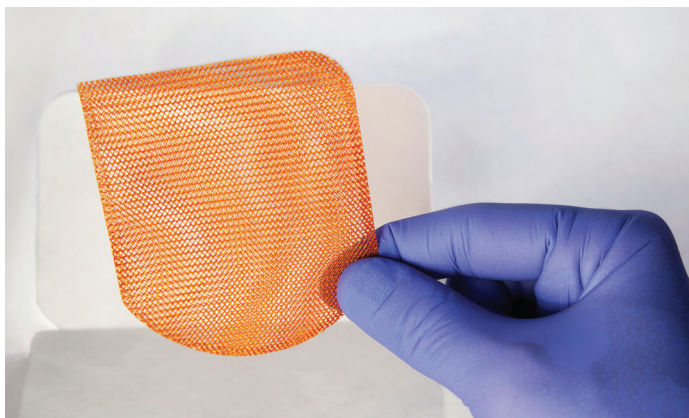
Characterize the rate of all system and/or procedure related adverse events which includes but is not limited to CIED infections, CIED migrations, or adverse events related to the TYRX Envelope.

PRIMARY ENDPOINT

Major CIED Infections:

TYRX Absorbable Antibacterial Envelope vs. Control 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 due to CIED Infection



Note: All other CIED Infections including superficial incisional Surgical Site Infections (SSIs) which meet the Center for Disease Control and Prevention (CDC) criteria, independent of the time from surgery, are defined as minor CIED Infections unless they meet the major CIED Infection criteria.

INCLUSION CRITERIA

- Subject is willing to sign and date the study PIC
- Subject is at least 18 years of age and meets age requirements per local law
- Subjects are scheduled for at least one of the following:
 - Subject has an existing CIED (any manufacturer) and is undergoing IPG (including CRT-P, ICD or CRT-D) replacement
 - Subject is undergoing an upgrade with a new Medtronic generator (including subjects planning to have leads added, or extracted and added)
- Subject will undergo a *de novo* or a Medtronic CRT-D system implant
- Subject has an existing study-eligible Medtronic CIED in which the pocket was not accessed within the last 365 days, and is undergoing pocket or lead revision
- Subject is willing to provide the contact information for the physician who provides follow-up care for his/her CIED

EXCLUSION CRITERIA

- Known allergy to minocycline or rifampin or their derivatives, or any other known contraindications to implantation of the TYRX Absorbable Antibacterial 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 (SLE), because minocycline has been reported to aggravate this condition
- Female patient who is pregnant (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.