A Randomized Noninferiority Study of the TYRX-A Antibacterial Envelope Alone Versus Envelope Plus Intraoperative Antibacterial Irrigant and Postoperative Oral Antibiotics to Prevent Cardiac Implantable Electronic Device Infections in High-Risk Patients

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1.0 Background

The number of cardiac implantable electronic devices (CIEDs) implanted each year has grown rapidly over the past two decades, largely due to expanding use of implantable cardioverter-defibrillators (ICDs) and devices capable of delivering cardiac resynchronization therapy (CRT).[8] CIEDs have increasingly been utilized in older patients with multiple medical comorbidities. As a result CIED infections, defined as infections involving the generator implant site (pocket) and/or intravascular leads, have become increasingly prevalent, with the rate of growth in infections outpacing that of CIED procedures.[9] The increase in incidence of CIED infections has outpaced the growth in device implantation, in large part due to the medical complexity of today's CIED patients.[9-11] These devastating complications are associated with significant cost, morbidity, and mortality.[4,9,12-14] The odds of both short term and long term mortality are at least doubled in patients who suffer CIED infections, and long term survival is particularly poor in women.[4,11,12]

CIED infection risk factor	References
Diabetes mellitus	1,2
Chronic kidney disease	1-4
Therapeutic anticoagulation	1,2,4
Chronic heart failure	4
Chronic corticosteroid use	5
Fever or leukocytosis	6
Device revision*	1,2,7
Three or more leads	5
Early re-operation	6,7
Prior device infection	5

Table 1: Established CIED infection risk factors. *Includes generator change, pocket revision, and lead revision.

Patient-specific risk factors for CIED infections have been examined in multiple registries and case-control studies and are presented in Table 1. For patients with at least two risk factors, the reported incidence of CIED infection is 2-3%.[1,14,15] Management of these infections is complex and expensive. The cornerstone of management is the complete removal of all infected hardware whenever possible, which in itself poses significant risks for patients.[16,17] **Therefore prevention of infections is crucial.**

Best practices for reducing CIED infections are an active area of research. Since most infections occur as a result of bacterial seeding at the time of device implantation or revision, careful attention to strict sterile technique is mandatory. Optimal skin preparation and perioperative intravenous antibiotics have been associated with a reduced rate of CIED infections in randomized controlled studies.[7,18] Additionally, several recent retrospective studies have suggested an important role of the minocycline and rifampin impregnated TYRX antibacterial envelope in reducing infections. The device consists of 2 polypropylene mesh sheets joined on 3 sides with a 3mm seam and is available in 2 sizes to accommodate pacemaker and ICD pulse

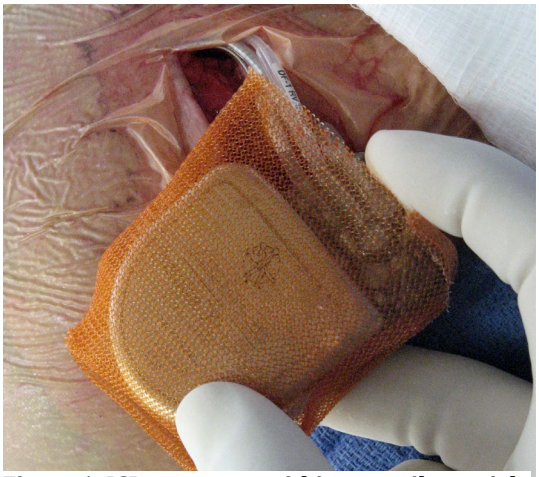

Figure 1: ICD generator within an antibacterial envelope just prior to implantation.

generators. This polypropylene envelope releases minocycline and rifampin from a bioresorbable polyarylate polymer over approximately 7 days, directly into the CIED generator pocket (Figure 1).

Aside from optimal skin preparation and perioperative intravenous antibiotics, other practices to reduce the risk of CIED infections vary widely. Many operators use an antibacterial solution (e.g., polymyxin-B/bacitracin) to irrigate the pocket during device implantation. Additionally, many centers have adopted the routine use of prophylactic postoperative antibiotics to reduce the risk of CIED infections. However, neither of these strategies has been evaluated in randomized clinical studies. Antibacterial irrigation solution is expensive, and oral antibiotics are associated with a small yet clinically important risk of adverse effects, including *Clostridium difficile* infection. Therefore, prospective randomized studies are needed to evaluate the efficacy, safety, and cost-effectiveness of intraoperative antibacterial rinse and postoperative oral antibiotics.

Summary of significance: CIED infections constitute major complications of device implantations or revisions and are becoming increasingly prevalent. Infections are associated with increased morbidity, mortality, and cost, and are very difficult to treat. Recent studies have explored ways to reduce the incidence of CIED infections, and use of the TYRX antibacterial envelope has emerged as a potential strategy for prevention. Other strategies including intraoperative antibacterial irrigation and postoperative oral antibiotics are commonly used despite the lack of prospective studies documenting efficacy, safety, and cost-effectiveness. We and others have reported a very low incidence (<1%) of CIED infections in high-risk patients receiving the TYRX antibacterial envelope. One intriguing possibility is that the antibacterial envelope can be used instead of intraoperative antibacterial rinse and postoperative oral antibiotics. Therefore, an important **knowledge gap** exists about the best practices to prevent CIED infections in high-risk individuals.

2.0 Rationale and Specific Aims

SPECIFIC AIM: to test the hypothesis that the use of the TYRX antibacterial envelope <u>alone</u> is noninferior to a strategy using the antibacterial envelope <u>and</u> intraoperative antibacterial irrigant <u>and</u> postoperative oral antibiotics for the reduction of cardiac implantable device infections in patients with ≥2 risk factors for infection.

CIED infections are devastating yet potentially preventable complications. We previously conducted a retrospective study of the TYRX antibacterial envelope and found that use of the device in patients with ≥2 risk factors for CIED infection was associated with a markedly decreased infection rate (0.4% with the device versus 3% without, adjusted odds ratio [95% confidence interval]: 0.09 [0.01 to 0.73], P =0.02). All patients in our previous study had intraoperative irrigation of the device pocket with polymyxin-B/bacitracin solution and received routine postoperative oral antibiotics consistent with local practices. However, whether use of intraoperative irrigant and

postoperative antibiotics reduces the risk of infection has not been evaluated in prospective, randomized trials. Moreover, it is unknown whether these treatments offer any *incremental benefit* over the use of the TYRX antibacterial envelope alone.

Given the significant cost of polymyxin-B/bacitracin solution and concerns over unnecessary use of oral antibiotics and emerging resistant microorganisms, it is critically important to establish whether these treatments offer any incremental benefit for patients at high risk for a CIED infection who are receiving the TYRX antibacterial envelope. The **Specific Aim** of this study will be to **prospectively test the hypothesis that an infection risk-reduction strategy using the TYRX antibacterial envelope alone is noninferior to a strategy using the envelope with intraoperative antibacterial irrigant and postoperative oral antibiotics in patients undergoing a CIED procedure who have at least 2 CIED infection risk factors.**

3.0 Previous Animal and Human Studies

The TYRX antibacterial envelope effectively prevented CIED infections in an animal model. In an animal model of direct bacterial inoculation into the device pocket, the TYRX antibacterial envelope showed excellent activity against *Staphylococcus epidermidis, Staphylococcus capitis, Escherichia coli, and Acinetobacter baumannii.*[19] Importantly, systemic levels of minocycline and rifampin were undetectable.

Use of the TYRX antibacterial envelope has been associated with a reduced incidence of CIED infections in retrospective studies of high-risk patients. In a multi-center trial, use of the TYRX antibacterial envelope was associated with a low risk of CIED infections (0.5%).[20] However, the relatively short follow-up period (mean: 1.9 months) and lack of a control arm limited the interpretation of the study's results. We conducted a retrospective controlled study of the TYRX antibacterial envelope in patients with at least 2 CIED infection risk factors at our institution. Among 260 TYRX envelope recipients, the incidence of CIED infection after a mean 18.7 month follow-up period was 0.4%, compared with 3% in 639 high-risk controls who did not receive the envelope (adjusted odds ratio: 0.09, 95% confidence interval 0.01 to 0.73, P =0.02).[15] Another retrospective study at a high-volume center found that the prevalence of CIED infections decreased from 1.5% to 0.6% after the TYRX antibacterial envelope was instituted into practice (P =0.03).[21]

Based on these and other studies, the Worldwide Randomized Antibiotic Envelope CIED Infection Prevention Trial (WRAP-IT) was conceived. This landmark trial prospectively evaluated the efficacy of the TYRX-A antibacterial envelope. However, our study is complementary to the WRAP-IT trial because we will specifically evaluate whether the TYRX-A antibacterial envelope alone offers ample protection against CIED infections without the use of intraoperative antibacterial solution and postoperative oral antibiotics.

4.0 Inclusion/Exclusion Criteria

Inclusion criteria	Exclusion criteria
Age ≥18 years old	Medical condition that is likely to be fatal in less than one year
Able to give informed consent	Emergent CIED procedure
At least 2 of the following risk factors for infection: • Diabetes mellitus • Chronic kidney disease (estimated creatinine clearance <30 ml/min • Therapeutic anticoagulation • Chronic heart failure • Chronic use of corticosteroids • Fever ≥38° C or leukocytosis (≥11,000 cells/mm^3) within 24 hrs of implant • Device revision (including generator change, or extraction) • ≥3 leads (receiving a new CRT system, current leads, or previously abandoned leads) • Early reoperation (pocket re-entry <2 weeks) • Previous CIED infection	Allergy to rifampin or minocycline Allergy to polymyxin-B, bacitracin, neomycin or amikacin
	Subject is pregnant
	Current CIED pocket infection

5.0 Enrollment/Randomization

General approach and study design: In a multicenter randomized controlled trial, we will recruit up to 1492 patients scheduled to undergo an elective CIED procedure with use of the TYRX-A antibacterial envelope. Using a parallel group design, patients will be randomized 1:1 to either:

1. intraoperative irrigation solution using bacitracin, that may also include neomycin, polymixin-B or amikacin, plus post-operative oral antibiotics (cephalexin, clindamycin, or levofloxacin; control arm)

OR

2. no intraoperative antibiotic irrigant/post-operative oral antibiotics (experimental arm).

Patients will be followed for CIED infections for a minimum of 180 days. The primary analysis will test whether the antibacterial envelope alone is noninferior to a strategy using the envelope and antibacterial irrigant and oral antibiotics.

Recruitment and retention: Patients will be enrolled at 4 high-volume centers: Vanderbilt University Medical Center in Nashville, Tennessee (the coordinating center), Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, The Valley Hospital in Ridgewood, New Jersey, and Cooper Health System in Camden, New Jersey. Additional sites may be added as needed. Patients will be screened from cardiology clinic schedules, electrophysiology lab schedules, and inpatient censuses. A research coordinator at each site will be responsible for screening, enrollment, and data collection. The principal investigator for each site will be responsible for the conduct of all study procedures with appropriate oversight from the institutional review board at each site.

Patients who are scheduled to undergo a de novo pacemaker or ICD implant, generator exchange, device, lead, or pocket revision, or re-implantation after a recent CIED infection will be screened for entry into the study. After careful consideration of inclusion and exclusion criteria, prospective participants will receive written and verbal information about the study from study personnel. Willing participants will be provided a written informed consent form, and after all questions have been answered, will be asked to sign the form.

Patients scheduled for CIED implantation with a device not manufactured by Medtronic Inc. will be considered for our study. In addition, de novo Medtronic Inc. non-CRT pacemaker and ICD implantations will be considered.

Patients with a current CIED pocket infection will be excluded since the TYRX antibacterial envelope is not indicated for the treatment of an active infection. However, patients with a recent infection, who have had successful CIED system explantation and are scheduled for implantation of a new CIED system (usually on the contralateral side of the chest) will be considered for inclusion in our study.

Randomization: Randomization will be performed at the coordinating center using a permuted block design with random block sizes of 2, 4, or 6 patients. Randomization will be stratified by center and by history of previous CIED infection.

6.0 Study Procedures

Device implantation and follow-up. CIED procedures will be performed in accordance with established practice guidelines. Perioperative procedures to reduce the risk of CIED infection including optimal skin preparation and intravenous antibiotics

(cefazolin or vancomycin) will be applied to all patients. All patients will receive the TYRX absorbable antibacterial envelope per routine care.

Patients randomized to the intraoperative antibacterial irrigant/postoperative oral antibiotic (control) arm will undergo irrigation of the device pocket with up to 1 liter of an antibiotic solution using bacitracin, that may also include neomycin, polymixin-B or amikacin, in accordance with the local hospital standard. Patients in the control arm will also receive 3 days of postoperative oral antibiotics (cephalexin 500mg 3 times daily, clindamycin 300mg 3 times daily, or levofloxacin 500mg once daily) as per investigator routine ordering practice with discretion per each individual patient. Patients randomized to the experimental arm will not receive intraoperative antibacterial irrigation (will be allowed up to 1 liter sterile saline irrigation), nor post-operative oral antibiotics.

All patients will be followed after their procedures according to established practice guidelines. At a minimum, patients will be seen 2-4 weeks after the procedure for a wound check, at 6 months, and then every year or more frequently as dictated by each patient's clinical status. For patients who are referred to a study center for their CIED procedure and follow-up with a local electrophysiologist a study coordinator will call the patient at 6 months to ascertain study endpoints and request a copy of the follow-up clinic visit note. We anticipate that this will apply to only a small minority (<10%) of study subjects. A digital photograph of the device pocket will be captured at the 2-4-week postoperative visit. In addition, the study nurse will telephone each patient 3 months after implantation to assess for symptoms and signs of infection. For the purposes of the study, patients will continue to be followed for a minimum of 6 months after the procedure, but additional follow-up data after six months may be collected continuously until the study closes.

Ascertainment of the primary endpoint: CIED infection after a minimum 6-month follow-up period. The primary study endpoint will be CIED infection resulting in complete CIED system removal, antibiotic therapy in patients who are not candidates for system removal, or death due to CIED infection. To avoid detection bias we will prospectively apply criteria for definition of the primary endpoint and ask treating physicians to thoroughly document objective findings (Table 2).

Table 2: Examples of objective signs of CIED infection.

Objective findings of CIED infection
*Fever or leukocytosis without an alternative explanation (e.g., urinary tract infection or pneumonia)
*Tenderness, erythema, or warmth at the pulse generator site
*Purulent discharge from the pulse generator site (from incision or fistula)
*Positive blood or pulse generator site cultures
*Vegetation adherent to CIED hardware
*Purulent material within pulse generator pocket upon reoperation

A digital photograph of the device pocket will be captured routinely at the 2-4 week postoperative visit and whenever CIED infection is a consideration. In case of a suspected CIED infection, treating physicians will be strongly encouraged to obtain peripheral blood cultures prior to initiation of antibiotic therapy and intraoperative cultures during CIED system removal per standard guidelines. A panel of 3 physicians at the coordinating center who are blinded to study assignment (experimental versus control) will independently adjudicate outcomes in "real time" and will vote whether or not the criteria for CIED infection have been met. A minor superficial infection of the incision that does not involve the generator pocket, does not result in any systemic symptoms or signs, and is treated with either observation or a short course of oral antibiotics, will not be counted as a CIED infection but will be considered a secondary endpoint.

Study oversight: The principal investigator at each study sight will be responsible for all aspects of the study at their respective sites. To ensure fidelity with the study protocol, an independent study coordinator at Vanderbilt University who is not directly involved with the study will review upon initiation of the study and first patient enrolled at each site, and then a random selection (10%) of patient records at each site (including Vanderbilt University) on a continuous basis set out by the monitoring agreement throughout the duration of the study, and quarterly prepare a report for the study's principal investigator.

7.0 Risks

Risks associated with the TYRX-A antibacterial envelope: The TYRX-A antibacterial envelope has been used extensively at each study site since 2009, and all implanting electrophysiologists are familiar with its use. The volume of the device generator pocket has to be expanded by approximately 10-20% to accommodate the envelope. This creates the potential for an increased risk of bleeding and hematoma, although these have not been quantified. Other potential risks of envelope use include allergic reaction and pain or discomfort at the generator site. Importantly, systemic levels of rifampin and minocycline were undetectable in animals that received the antibacterial envelope in a previous study.[19] The previous generation, non-absorbable envelope was associated with increased scarring within the generator pocket that posed difficulty with explantation in a minority of cases. The absorbable envelope to be used in the current study was developed with this limitation in mind and should reduce scarring, although this requires further study. In summary, the antibacterial envelope has been implanted in thousands of patients to date and has been associated with a very low incidence of adverse events.

Risks associated with polymyxin-B: Although parenteral use of polymyxin-B is associated with significant adverse effects, the risks associated with intraoperative irrigation are largely undefined but believed to be minimal.

Risks associated with neomycin: The most common adverse reactions to oral neomycin are nausea, vomiting and diarrhea. However, the risks associated with intraoperative irrigation are thought to be minimal.

Risks associated with amikacin: Approximately 1-10% experience neurotoxicity, nephrotoxicity and ototoxicity. Less than 1% experience hypotension, headache, rash, nausea, vomiting, tremors, arthralgia, weakness and allergic reacting. However, the risks associated with intraoperative irrigation are believed to be minimal.

Risks associated with bacitracin: The topical use of bacitracin is generally safe but has been associated with rare incidents of allergic reactions and anaphylaxis. Systemic use of bacitracin is associated with rash, albuminuria, nausea, vomiting, azotemia, nephrotoxicity, pain at injection site, renal failure, and anaphylaxis. The risks associated with intraoperative irrigation with bacitracin solution are largely undefined but thought to be minimal due to little, if any, systemic absorption.

Risks associated with cephalexin: Risks include agitation, confusion, dizziness, fatigue, hallucination, headache, erythema multiforme (rare), genital pruritus, skin rash, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare), urticaria, abdominal pain, diarrhea, dyspepsia, gastritis, nausea (rare), pseudomembranous colitis, vomiting (rare), genital candidiasis, vaginal discharge, vaginitis, eosinophilia, hemolytic anemia, neutropenia, thrombocytopenia, cholestatic jaundice (rare), hepatitis (transient, rare), increased serum aminotransferase levels, anaphylaxis, angioedema, hypersensitivity reaction, arthralgia, arthritis, arthropathy, and interstitial nephritis (rare).

Risks associated with clindamycin: Risks include cardiac arrest (rare; IV administration), hypotension (rare; IV administration), thrombophlebitis (IV), metallic taste (IV), acute generalized exanthematous pustulosis, erythema multiforme (rare), exfoliative dermatitis (rare), maculopapular rash, pruritus, skin rash, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis, urticaria, vesiculobullous dermatitis, abdominal pain, antibiotic-associated colitis, *Clostridium difficile* associated diarrhea, diarrhea, esophageal ulcer, esophagitis, nausea, pseudomembranous colitis, unpleasant taste (IV), vomiting, azotemia, oliguria, proteinuria, vaginitis, agranulocytosis, eosinophilia (transient), neutropenia (transient), thrombocytopenia, abnormal hepatic function tests, jaundice, anaphylactoid reaction (rare), DRESS syndrome, abscess at injection site (IM), induration at injection site (IM), irritation at injection site (IM), pain at injection site (IM), polyarthritis (rare), and renal insufficiency (rare).

Risks associated with levofloxacin: Risks include chest pain (1%), edema (1%), headache (6%), insomnia (4%), dizziness (3%), skin rash (2%), pruritus (1%), nausea (7%), diarrhea (5%), constipation (3%), abdominal pain (2%), dyspepsia (2%), vomiting (2%), vaginitis (1%), candidiasis (1%), injection site reaction (1%), and dyspnea (1%). The following adverse reactions have been noted in less than 1% of cases: abnormal electroencephalogram, abnormal gait, acute renal failure, ageusia,

agranulocytosis, anaphylactoid reaction, anemia (including aplastic and hemolytic), anorexia, anosmia, brain disease (rare), cardiac arrest, cardiac arrhythmia (including ventricular tachycardia/fibrillation and torsades de pointes), *Clostridium difficile*-associated diarrhea, confusion, convulsions, crystalluria, cylindruria, depression, elevation in serum levels of skeletal-muscle enzymes, eosinophilia, epistaxis, erythema multiforme, esophagitis, exacerbation of myasthenia gravis, gastritis (including gastroenteritis), glossitis, granulocytopenia, hallucination, hepatic failure (some fatal), hepatic insufficiency, hepatitis, hyperglycemia, hyperkalemia, hyperkinesias, hypersensitivity reaction (including anaphylaxis, angioedema, rash, pneumonitis, and serum sickness), hypertension, hypertonia, hypoacusis, hypoglycemia, hypotension, increased INR, increased intracranial pressure, increased serum alkaline phosphatase, increased serum transaminases, interstitial nephritis, intestinal obstruction, jaundice, leukocytosis, leukopenia, leukorrhea, lymphadenopathy, multiorgan failure, muscle injury, muscle spasm, pancreatitis, pancytopenia, paralysis, paranoia, peripheral neuropathy (may be irreversible), phlebitis, phototoxicity, prolonged prothrombin time, prolonged QT interval on ECG, pseudotumor cerebri, psychosis, renal function abnormality, rhabdomyolysis, rupture of tendon, scotoma, seizure, skeletal pain, skin photosensitivity, sleep disorder (including abnormal dreams and nightmares), Stevens-Johnson syndrome, stomatitis, suicidal ideation, syncope, tachycardia, tendonitis, toxic epidermal necrolysis, toxic psychosis, thrombocytopenia (including thrombotic thrombocytopenic purpura), uveitis, vasculitis (leukocytoclastic), vasodilatation, visual disturbances(including diplopia), and voice disorder.

8.0 Reporting of Adverse Events or Unanticipated Problems Involving Risk to Participants or Others

All serious related adverse events and incidents of noncompliance with the protocol will be reported to the institutional review board and coordinating center. For the purposes of the study, serious adverse events will only be documented if there is a reasonable suspicion that they are related to the envelope, procedure, infection, or death. A serious adverse event will be defined as an untoward medical occurrence that results in death, is life-threatening, requires hospitalization, results in persistent or significant disability, or requires intervention to prevent permanent disability or death. Other untoward medical occurrences that do not meet the above criteria will be classified as adverse events. Study personnel will monitor for adverse events. All suspected or confirmed adverse events will promptly be reported to the principal investigator, who will collect data on these occurrences. The principal investigator will report unexpected and related serious adverse events to the institutional review board, coordinating center, and any other applicable authority, within 10 days of knowledge of the occurrence or sooner depending on local IRB policy. If a death occurs, it will be reported within 24 hours of knowledge of the death. The principal investigator will report unrelated serious and non-serious adverse events to the institutional review board on an annual basis per local IRB policy. Non-serious adverse events will be reported at the time of continuing review per local IRB policy.

Each site will be required to have a local study coordinator who will be responsible for entering the study information into the web-based database and uploading the identifiable source documents/medical records associated with the study information.

In addition, identifiable source documentation verifying all collected study data points will be securely uploaded into the web-based database.

9.0 Study Withdrawal/Discontinuation

Participation in the study is strictly voluntary, and patients will be able to withdraw at any time. Following the subject's withdrawal, no further data will be collected, although any analyzed data will be maintained.

10.0 Statistical Considerations

We conducted a sample size/power calculation based on both frequentist and Bayesian methods. These calculations were performed by Ms. Hui Bian and Ms. Yanna Song and overseen by Dr. Chang Yu, Ph.D. in the Vanderbilt University Department of Biostatistics. Based on our previous clinical experience, we estimate the infection rate in the control group to be 1%. Using frequentist methods and a noninferiority limit of 1%, we will need to recruit 1492 subjects to have 80% power to show noninferiority at an alpha level of 0.05. We also conducted a simulation using a Bayesian flexible design analysis. We again assumed a 1% event rate among controls and a noninferiority limit of 1%. In the simulation the odds of being able to claim noninferiority were 0.88 with an average sample size of 1492 subjects. This approach offers the distinct advantage of being able to stop enrollment early once the threshold for noninferiority is reached. We plan to conduct regular interim analyses, beginning after 600 patients are enrolled and complete the minimum follow-up period. Therefore, it will be feasible to conduct our proposed trial in 3-3.5 years.

11.0 Privacy/Confidentiality Issues

All research hard copy records will be stored in a locked cabinet within a locked office with access only to the research personnel. Study data will be stored in the secure Research Data Capture (REDCap) database. Only the investigators, staff and study monitors will have access to the study data.

12.0 Follow-up and Record Retention

We expect enrollments for 30 months with additional 6 months for follow up on last enrolled subject. Then there will be additional 6 months of record retention after the last patient enrolled reaches 6 months post op. All data will be archived and stored indefinitely.

Schedule of Events

Study Procedure Schedule	Baseline	CIED Procedure Day	For 3 days Post-op	Wound check-approximately 4 weeks post-procedure (+/1-2 weeks)	3 month Phone Call f/u	6 month Visit / or Phone Call	Unscheduled/Suspected CIED Infection	Yearly/end of study
Office Visit/History/Physical Exam [a]	x			x		x[a]	x	x
Informed Consent	x							
Data collection of routine pre-op labs (ie. CBC/CMP)	x							
CIED Device Implant with TYRX absorbable antibacterial envelope		x						
Randomization		x						
Irrigation of device pocket [b]		x						
Prescription for 3 days of postoperative oral antibiotics [c]		x	x					
Digital Photograph of device pocket				x			x	
Signs and symptoms of infection check					x		x	x
Adjudicate Criteria for CIED infection[d]							x	
peripheral blood cultures							x	
Intraoperative cultures during CIED system removal							x	
Antibiotic Medication Documentation							x	

All patients will be followed after their procedures according to established practice guidelines. At a minimum, patients will be seen 4 weeks after the procedure for a wound check, at 6 months, and then every year or more frequently as dictated by each patient's clinical status

[a] ONLY at the 6 month time point, if the patient cannot be reached after 2 phone calls and a letter, a chart review can be done to retrieve the data needed for the visit

[b] ONLY patients randomized to Control Arm will receive irrigation of the device pocket with up to 1 liter of antibiotic wash

[c] ONLY patients randomized to Control Arm will receive 3 days of postoperative oral antibiotics (cephalexin 500mg 3 times daily, clindamycin 300mg 3 times daily, or levofloxacin 500mg once daily)

[d] A panel of 3 physicians at the coordinating center who are blinded to study assignment (experimental versus control) will independently adjudicate outcomes in "real time" and will vote whether or not the criteria for CIED infection have been met.

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