**National Evaluation System for health Technology Coordinating Center (NESTcc)**

# NESTcc PROJECT PROPOSAL

## Administrative Information

| Required Field | Information |
|---|---|
| Project ID | NESTcc Test Case 07 Phase 2 |
| Test-Case Name/Project Title | Indication Extension for Medical Devices Using RWE from NESTcc Network Collaborators: Safety and Effectiveness of Cardiac Ablation of Persistent Atrial Fibrillation and Ischemic Ventricular Tachycardia using ThermoCool Catheters |
| Medical Device or Technology of Interest | ThermoCool cardiac ablation catheters |
| Participating Network Collaborators (list all) | Mercy, Mayo Clinic |
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## Research Approach

**Network Collaborators**

**Contributing Roles**

| Project Partners | Contributing Role |
|---|---|
| Mercy | *Data site; project coordination, study design and analysis; reporting lead* |
| Mayo Clinic | *Data site; study design and analysis; and feedback on reporting* |
| Johnson & Johnson | *Study concept; study design and analysis; and feedback on reporting* |

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# 1 Background

Recent policy changes and advances in the availability of real-world data (RWD) have increased the salience of the use of RWD collected during routine clinical care to generate real-world evidence (RWE) to support regulatory decision-making [1]. The 21st Century Cures Act of 2016 placed increasing emphasis on the use of RWE, including for the approval of a new indication for an approved drug [2]. In 2017, the FDA Center for Devices and Radiological Health (CDRH) released a Guidance on "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," which discusses the potential use of RWE to support expanded indications for use for medical devices [3]. Examples of using RWE for this purpose include several premarket indication expansion decisions based on data from the Transcatheter Valve Therapy Registry [4]. In March 2021, the FDA CDRH released a report with 90 examples of regulatory submissions that successfully used RWD/RWE to support regulatory decisions [5]. Many examples used registries. However, registries are specialized RWD sources because they require significant effort and resources, including general reliance upon trained abstractors to manually extract and input many data elements [6]. In addition, registries are usually specialized to a certain disease or condition with a limited number of variables due to the cost and time needed for data abstraction and, therefore, are unavailable for all medical devices.

To advance the goal of developing timely and robust RWE for informing regulators, clinicians, and patients regarding the effectiveness and safety of medical devices, the National Evaluation System for health Technology (NEST) was created [7]. In August 2016, the FDA awarded a grant to the Medical Device Innovation Consortium (MDIC) to establish a Coordinating Center for NEST (NESTcc). The most ubiquitous RWD sources with the greatest clinical detail are health system databases, including electronic health records (EHR). However, health system data are not specifically designed for research purposes and their ability to contribute reliable evidence for medical device safety and effectiveness evaluations, including for label expansions, remains uncertain. The NESTcc has supported multiple test case studies to investigate the use of RWD, including health system data, in RWE generation that can be used to inform regulatory decision-making. These feasibility assessments have focused on the availability of pertinent variables – including medical device use, procedure of interest, covariates, and safety and effectiveness outcomes [8].

The study was proposed to the NESTcc by Johnson & Johnson, with the objective of evaluating the safety and effectiveness of two cardiac ablation catheters when used in routine clinical practice. The specific catheters of interest are the ThermoCool Smarttouch® (ST) catheter, initially approved by FDA in February 2014, and the ThermoCool Smarttouch® Surround Flow® (STSF) catheter, initially approved by FDA in August 2016.

After independent review, the project was funded by the NESTcc. NESTcc currently has 15 Network Collaborators (health care providers, academic research institutions, payers, and professional registries) that collect, curate, and analyze RWD, which may be used for regulatory decision-making (https://nestcc.org/research-network/#network-collaborators). Among its Network Collaborators, NESTcc identified the 3 health systems that were interested in the proposal and that had significant experience with these devices: Mercy Health, Mayo Clinic, and Yale-New Haven Hospital (YNHH). Johnson & Johnson and the 3 NESTcc Network Collaborators, with Mercy Health serving as the lead, developed a full research plan that was approved by the NESTcc.

The goal of the initial phase of the first portion of the study was to assess the feasibility of using the 3 independent health systems to obtain RWD from their electronic information systems, including EHRs, to compare the safety and effectiveness of the ThermoCool ST catheter to the ThermoCool STSF catheter for persistent atrial fibrillation (AF). The ThermoCool STSF catheter has an improved irrigation technology, called Surround Flow® (SF) to the tip of the ThermoCool cardiac ablation catheter. Both catheters have labeled indications for treating paroxysmal AF. Only ThermoCool STSF is labeled for persistent AF, which was obtained by an investigational device exemption (IDE) clinical trial (PRECEPT) [9]. The second portion of the study was to assess the feasibility of the 3 independent health systems to obtain RWD from their electronic information systems, including EHRs, to compare the safety and effectiveness of the ThermoCool STSF catheter with the ThermoCool ST catheter for ischemic ventricular tachycardia (VT); the latter catheter has a labeled indication for recurrent drug/device refractory sustained monomorphic VT due to prior myocardial infarction (MI), while the ThermoCool STSF catheter does not.

The feasibility assessment first sought to identify the medical devices (ablation catheters) of interest in the health system electronic information systems and then to link to the pertinent patient populations who received treatment with these catheters. Afterwards, the performance of codes/algorithms to identify key safety and effectiveness outcomes of interest (ischemic stroke, cardiac tamponade, acute heart failure, and arrhythmia-related hospitalization) was compared to clinician chart review in a small sample of patients at each health system (up to 25 patients per system). All analyses were conducted individually at each health system using a decentralized model; [10] summary results were shared across researchers from the three institutions, but no patient-level data were shared.

# 2 Study Description

The NESTcc Test Case 07 titled "The Feasibility of Using Real-World Data in the Evaluation of Cardiac Ablation Catheters" was completed as of March 2020. The feasibility stage or phase of the study identified that the necessary data elements could be ascertained in the EHR systems of the NESTcc Network Collaborators who elected to participate in this NESTcc test case. The next stage of the study, which we refer to as phase 2, will test the study hypotheses for an actual label expansion study using EHR databases that, if the data indicate the necessary product-related safety, will be submitted to the FDA CDRH Office of Health Technology 2 (Electrophysiology).

In the feasibility study phase, the 3 NESTcc Network Collaborators (NCs) (Mercy, Mayo Clinic and YNHH), and Johnson & Johnson successfully identified the use of ThermoCool catheters using unique device identifiers (UDIs) captured by barcode scanning at point of care and charge codes for device billing with detailed device information (Mercy) and supply chain and inventory system databases with UDIs captured by barcode scanning and registry data (Mayo Clinic and YNHH) in the NCs' EHR systems. In an evaluation of the follow up rates of patients who have undergone a cardiac ablation procedure as part of the feasibility study, excellent rates of follow up in Mercy and Mayo Clinic healthcare systems were found. However, low rates of follow up were identified in the YNHH system (Appendix 5 provides more detail). Consequently, the YNHH system is not used as a NESTcc Network Collaborator site for the hypothesis-testing phase of this study. In the feasibility phase of the study, the study investigators were careful to ensure that no analyses of the analytical dataset that will be used for the hypothesis testing were conducted, especially those that assessed the rates of study endpoints in the study groups or compared the study groups to comparator groups.

For the ThermoCool ST catheter to expand its indication for the treatment of persistent AF, we propose the use of the ThermoCool STSF catheter that was recently approved for the persistent AF indication as the comparator.

For the treatment of ischemic VT (defined by the presence of a history of MI prior to the index ablation procedure in this study) using the 56-hole irrigated ThermoCool STSF catheter, we originally proposed the use of the ThermoCool ST catheter as a comparator, since it already has an indication for ischemic VT. In consideration of the relatively small sample size, inadequate covariate balance achieved by propensity score methods, and the possibility of zero events in one or more catheter groups due to the small sample size in the ischemic VT populations in the Mercy and Mayo Clinic databases, we propose the use of a single arm design to compare the cumulative incidence of a composite safety endpoint to a performance goal (as suggested in the paper by Lu et al. 2020 [11]) among patients with ischemic VT who had a procedure performed with the ThermoCool STSF catheter (pooled across Mercy and Mayo Clinic) for hypothesis testing.

# 3 Study Aims

The specific aims are to use retrospective RWD from the electronic data systems at Mercy and Mayo Clinic to:

- Evaluate the non-inferiority of the ThermoCool ST catheter to the ThermoCool STSF catheter on a composite safety endpoint for persistent AF and
- Compare the cumulative incidence of a composite safety endpoint to a performance goal for ischemic VT among those who had a procedure performed with the ThermoCool STSF catheter (pooled across patients from the Mercy and Mayo Clinic healthcare systems).

The first sought indication expansion is for the ThermoCool ST catheter to treat persistent AF. The ThermoCool ST catheter does not have an FDA-approved label to treat persistent AF whereas the ThermoCool STSF catheter does. An IDE clinical study (PRECEPT Trial) was conducted for a label expansion for the ThermoCool STSF catheter for persistent AF [9] and approved on September 30, 2020 under PMA supplement P030031/S100. This NESTcc test case study will compare the safety of ThermoCool ST when used for ablation to treat persistent AF to that of ThermoCool STSF as the comparator, thereby expanding the labelled indication for persistent AF for ThermoCool STSF to ThermoCool ST (**Table 1**).

The second indication expansion is for the ThermoCool STSF catheter to include an indication for the treatment of ischemic VT. The ThermoCool ST catheter has a label for ischemic VT. Among patients with ischemic VT who had procedures performed with the ThermoCool STSF catheter, this study will compare the cumulative incidence of a composite safety endpoint to a performance goal for expanding the indications of ThermoCool STSF to treat ischemic VT. This study will also perform a descriptive analysis for the safety endpoint among patients with ischemic VT who had procedures performed with the ThermoCool ST catheter for contextualizing the ThermoCool STSF results (**Table 1**).

As suggested by FDA, the primary objective will focus on safety, rather than effectiveness as the differences between the ThermoCool ST catheter and the ThermoCool STSF catheter are not expected to affect the device effectiveness for the treatment of persistent AF or ischemic VT.

Several exploratory objectives are also included, as described in the Study Objectives section of this protocol.

# 4 Study Objectives

## 4.1 Primary Objectives:

1) To evaluate if the ThermoCool ST catheter is non-inferior to the ThermoCool STSF catheter for the treatment of persistent AF on a composite safety endpoint in real-world settings

2) To evaluate ablation with the ThermoCool STSF catheter relative to a performance goal for the treatment of ischemic VT on a composite safety endpoint in real-world settings

## 4.2 Exploratory Objectives:

- To describe the effectiveness of ablation with the ThermoCool ST catheter relative to ThermoCool STSF for the treatment of persistent AF on a composite effectiveness endpoint in real-world settings using the propensity score balanced data

- To describe the effectiveness of ablation with the ThermoCool STSF catheter for the treatment of ischemic VT on a composite effectiveness endpoint in real-world settings using the unadjusted data

- To describe the safety of ablation with the ThermoCool STSF catheter for the treatment of overall VT on a composite safety endpoint in real-world settings using the unadjusted data. The overall VT population will be identified using the same criteria as ischemic VT except removing the requirement of prior MI

- To describe the safety of ablation with the ThermoCool STSF catheter for the treatment of ischemic VT on a composite safety endpoint in a subgroup that excludes non-ischemic cardiomyopathy patients using the unadjusted data

- To explore the sensitivity of the safety results for ischemic VT by performing an outcome analysis comparing the ThermoCool STSF group to the ST group using the propensity score balanced data

- To perform exploratory subgroup analyses among patients with a prior prescription of class I or III AAD before the index ablation procedure for the persistent AF population using the propensity score balanced data

**Table 1. Proposed indication expansions for ThermoCool catheters and proposed comparators**

| Devices of Interest | Approved Indications | Indication Expansion of Interest | Proposed Comparator Group |
|---|---|---|---|
| ThermoCool Smarttouch® Catheter (Approved in February 2014) | • Drug refractory recurrent symptomatic paroxysmal atrial fibrillation<br>• Type I atrial flutter in patients 18 years of age or older<br>• Recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults | Persistent AF | ThermoCool Smarttouch® SF, which has an FDA-approved label for persistent AF |
| ThermoCool Smarttouch® SF Catheter (Approved in August 2016) | • Drug refractory recurrent symptomatic paroxysmal atrial fibrillation<br>• Type I atrial flutter in patients 18 years of age or older<br>• Drug refractory recurrent symptomatic persistent atrial fibrillation (defined as continuous atrial fibrillation that is sustained beyond 7 days but less than 1 year), refractory or intolerant to at least one Class I or III antiarrhythmic medicine (approved on September 30, 2020) | Ischemic VT | A performance goal (twice the expected rate in the ThermoCool Smarttouch reference group)<br><br>ThermoCool Smarttouch, a 6-hole irrigated catheter with an FDA-approved indication for ischemic VT |

# 5 Research Methods

## 5.1 Data Source(s)

Mercy and Mayo Clinic electronic databases contain the information on demographics, encounters, procedures, diagnoses, supplies (including ThermoCool catheters), vitals, medications, laboratory and diagnostic procedures. These two health systems use Epic-based EHRs. In these EHR system databases, patient cohorts, diagnoses, procedures, and outcomes are identified based on medical billing, diagnosis, and/or procedure codes and algorithms. The codes and algorithms are identified through reviews of the literature and reports from the Sentinel Initiative's Health Outcome of Interest Validations and Literature Reviews (https://www.sentinelinitiative.org/sentinel/surveillance-tools/validations-lit-review) and further evaluated by clinical expert reviews and/or manual chart reviews.

- ### Mercy EHR System Database

Mercy is an integrated delivery network located in 4 states in the US Midwest region (Missouri, Kansas, Oklahoma, Arkansas) and headquartered in St. Louis, Missouri. The Mercy network includes approximately 45 hospitals, with a total of 4,148 staffed beds ranging from small, critical-access rural facilities to large, tertiary-care urban medical centers [12], and 350 outpatient facilities as well as 3,000 integrated providers.

Mercy, a leader in the incorporation of UDIs into an EHR system, conducted an FDA-sponsored demonstration whereby prototype UDIs of coronary stents were implemented in its electronic information systems for safety surveillance and research [12-14]. Mercy operates an EHR system that links the Epic-based EHR to the supply chain data through Mercy's OptiFlex (Omnicell) point of care barcode scanning inventory management system for devices since 2016. For devices used after 2016, devices are identified using UDIs and device catalogue numbers of the devices captured from its OptiFlex barcode scanning system at point of care. For devices used before 2016, devices are identified using a

combination of Healthcare Common Procedure Coding System (HCPCS) codes and Mercy-specific charge codes for device billing in the EHR. Device data are joined with ablation procedure data based on patient ID and procedure dates with encounter ID. Patient-specific data are from the Mercy's EpicCare EHR through Epic Clarity (the Epic data warehousing utility) and supplemental mortality data from the Social Security Death Master File [12]. The EHR system contains clinical information about patients who have undergone procedures such as cardiac ablation, treatments, and visits at facilities within the Mercy network since 2011.

Mercy has a network of healthcare providers and facilities within a specific geographic region that offers a full range of healthcare services and thus has good long-term follow-up. In a recent assessment for index ablations that occurred between 1/1/2014 and 3/31/2021, the percentages of follow-up (which included both face-to-face visits and remote contact, such as telephone visits) were 98.2% for ≥7 days, 96.2% for ≥30 days, 90.2% for ≥3 months, 82.1% for ≥6 months, and 68.4% for ≥1 year for persistent AF; and 97.7% for ≥7 days, 94.7% for ≥30 days, 90.2% for ≥3 months, 84.9% for ≥6 months, and 74.2% for ≥1 year for VT. Of note, the completeness of follow-up was determined by encounters within a time window around the follow up time. This may underestimate true follow-up rates since not all members may have had an in-person encounter/telephone visit with the healthcare system during those dates but still be a member of the healthcare system.

- ### Mayo Clinic EHR System Database

Mayo Clinic has major campuses in Rochester, Minnesota; Scottsdale and Phoenix, Arizona; and Jacksonville, Florida (https://www.mayoclinic.org/about-mayo-clinic). Mayo Clinic is a health system of 23 hospitals and 159 clinics, serving a population of approximately 2.3 million patients (https://nestcc.org/research-network/#network-collaborators).

UDIs are documented in two health IT systems at Mayo Clinic [15]. The UDI-linked device data after May 2018 when Epic EHR system was introduced at Mayo Clinic are documented in the Supply+ (Cardinal Health) and Plummer (Epic), which have worked together to standardize multiple clinical and business processes to improve efficiency and optimize inventory. Supply+ (Cardinal Health) is an enterprise-wide, integrated inventory management system to implement standardized surgical and procedure inventory management. Historical device data dating back to January 2014 are documented in the Mayo Clinic supply chain management system known as SIMS, which was a Mayo-designed and supported system to improve surgical case management and Mayo Group Practices across Mayo enterprise.

The percentages of follow-up were also high in the Mayo Clinic EHR system database: 99.6% for ≥7 days, 96.5% for ≥30 days, 92.5% for ≥3 months, 82.0% for ≥6 months, and 69.7% for ≥1 year for persistent AF; and 99.4% for ≥7 days, 96.3% for ≥30 days, 90.5% for ≥3 months, 82.6% for ≥6 months, and 71.4% for ≥1 year for VT in a recent assessment for index ablations that occurred between 1/1/2014 and 3/31/2021 and included all four Mayo sites (Rochester, Minnesoda; Scottsdale and Phoenix, Arizona; and Jacksonville, Florida).

Due to the low statistical power of the Mercy and Mayo Clinic databases to assess the hypothesis test of ThermoCool STSF to treat VT among patients with prior MI, a third supplemental database will be used to supplement these two databases if the FDA considers the Premier database fit for purpose.  A subsequent protocol amendment will be provided describing the Premier database relevance and reliability and the proposed analysis plan.

- ### Comparison of Demographic Characteristics of Patients in Mercy and Mayo Clinic EHR System Databases with Other U.S. National Healthcare Databases

Below is the comparison of age, sex, and race distribution of persistent AF patients who underwent an intracardiac catheter ablation of AF by pulmonary vein isolation from **1/1/2016 to 06/30/2020** (**Table 2a**) and VT patients who underwent an intracardiac catheter ablation of VT from **1/1/2014 to 06/30/2020** (**Table 2b**) among Mercy EHR system database, Mayo Clinic EHR system database, Premier Healthcare Database (US inpatient & outpatient hospital encounter data [>1,000 hospitals; 25% of US discharges annually; >220 million since 2000]), and Optum EHR database (US patient-level EHRs from integrated delivery networks [30 million patients annually; >100 million since 2006]). Mercy and Mayo Clinic EHR system databases are generally representative of the U.S. population of persistent AF and VT patients who had a cardiac ablation procedure.

**Table 2a.** Comparison of age, sex, and race distribution of **persistent AF** patients who had an intracardiac catheter ablation procedure among the 4 U.S. databases

| | Optum EHR | Premier | Mercy EHR | Mayo Clinic |
|---|---|---|---|---|
| **Characteristic** | % | % | % | % |
| Age categories, years | | | | |
| 18–49 | 6 | 5 | 6 | 6 |
| 50–59 | 20 | 18 | 17 | 20 |
| 60–69 | 39 | 38 | 40 | 39 |
| 70+ | 35 | 39 | 36 | 35 |
| Sex | | | | |
| Female | 28 | 31 | 29 | 27 |
| Male | 71 | 69 | 71 | 73 |
| Race | | | | |
| White | 93 | 91 | 96 | 97 |
| Black | 3 | 4 | 2 | 1 |
| Other/Unknown | 4 | 6 | 3 | 2 |

*Time period: 1/1/2016 to 06/30/2020 for the persistent AF population

**Table 2b.** Comparison of age, sex, and race distribution of **VT** patients who had an intracardiac catheter ablation procedure among the 4 U.S. databases

| | Optum EHR | Premier | Mercy EHR | Mayo Clinic |
|---|---|---|---|---|
| **Characteristic** | % | % | % | % |
| Age categories, years | | | | |
| 18–49 | 20 | 17 | 14 | 25 |
| 50–59 | 21 | 19 | 13 | 21 |
| 60–69 | 29 | 30 | 34 | 28 |
| 70+ | 31 | 34 | 39 | 26 |
| Sex | | | | |
| Female | 26 | 27 | 22 | 26 |
| Male | 74 | 73 | 78 | 74 |
| Race | | | | |
| White | 87 | 81 | 95 | 92 |
| Black | 6 | 8 | 3 | 2 |
| Other/Unknown | 7 | 11 | 2 | 6 |

*Time period: 1/1/2014 to 06/30/2020 for the VT population

## 5.2 Study Design and Population

- ### Study Design

This is a retrospective cohort study evaluating the safety of ablation with the ThermoCool ST catheter in usual clinical practice for persistent AF using a non-inferiority design with a pre-specified non-inferiority margin comparing the subject device (ThermoCool ST) to the comparator device (ThermoCool STSF) with respect to the risk difference using data balanced on pre-specified measured covariates. For ischemic VT, this retrospective cohort study will compare the cumulative incidence of a composite safety endpoint in the subject device group (ThermoCool STSF) to a performance goal using the unadjusted data.

Retrospective cohort analyses will also be conducted for exploratory objectives described above (section 4.2). No statistical comparisons will be made for exploratory analyses (ie, without hypothesis testing). Point estimates for the cumulative incidence and their confidence intervals within each group and for the risk difference between the groups will be provided.

- **Study Population**

The study consists of two separate patient populations (persistent AF and ischemic VT) for the evaluation of the primary objectives.

## 5.2..1. **Persistent AF Population**

### 5.2..1.1. ***Inclusion Criteria***

The inclusion/exclusion criteria for the persistent AF population consist of including patients meeting all the following:

- Underwent an intracardiac catheter ablation for AF by pulmonary vein isolation
- Had a primary or secondary diagnosis of persistent AF associated with the same intracardiac catheter ablation procedure encounter
- The index procedure for a patient is the first recorded intracardiac catheter ablation for AF by pulmonary vein isolation with a primary or secondary diagnosis of persistent AF.
- Index procedure performed using the ThermoCool ST catheter or the ThermoCool STSF catheter
- At least 18 years of age or older at the time of the index procedure
- At least 6 months of encounter history prior to the index procedure

### ***5.2..1.2. Exclusion Criteria***

And excluding individuals meeting any of the following:

- Received both the device of interest (ThermoCool ST catheter) and the comparator device (ThermoCool STSF catheter)
- Underwent an intracardiac catheter ablation prior to the index procedure
- Had a surgical cardiac ablation any time prior to or at the same time as the index procedure
- Had a concomitant left atrial appendage occlusion procedure at the time of the index procedure
- Had a concomitant atrioventricular node ablation at the time of the index procedure
- Had a prior heart transplant or long-term heart assist system implantation prior to the index procedure

Persistent AF patients will be identified by combining intracardiac catheter ablation procedure codes of AF ablation by pulmonary vein isolation (CPT code 93656 or ICD-10-PCS codes 025S3ZZ or 025T3ZZ) with ICD-10-CM diagnosis codes of persistent AF (I48.1, I48.11, and I48.19) associated with the same intracardiac catheter ablation procedure encounter.

An evaluation of the performance of this algorithm to identify persistent AF patients from the EHR system was conducted at Mercy and Mayo Clinic through a manual chart review process by cardiac electrophysiologists in a random sample of non-study population patients in this NESTcc test-case study and obtained high positive predictive values (PPVs) for a diagnosis of persistent AF either in a primary or secondary position (90% at Mercy and 89% at Mayo Clinic).

Usually, the threshold is 80% for a good PPV and 90% for an excellent PPV in RWD studies. A PPV of 80% has been accepted previously by the FDA as the minimum threshold (see Table 3.3.1.2.8. in the review of Epidemiology: Review of Extended-Release/Long-Acting (ER/LA) Opioid Analgesic PMR 3033-7 Final Study Report https://www.fda.gov/media/141356/download).

## 5.2..2. **Ischemic VT Population**

### 5.2..2.1. ***Inclusion Criteria***

The inclusion/exclusion criteria for the ischemic VT population consist of including patients meeting all the following:

- Underwent an intracardiac catheter ablation for VT
- Had a primary or secondary diagnosis of VT associated with the same intracardiac catheter ablation procedure encounter
- The index procedure for a patient is the first recorded intracardiac catheter ablation for VT with a primary or secondary diagnosis of VT

- Index procedure performed using the ThermoCool STSF catheter or the ThermoCool ST catheter
- At least 18 years of age or older at the time of the index procedure
- At least 6 months of encounter history prior to the index procedure
- Any MI diagnosis prior to the index procedure

#### *5.2..2.2. Exclusion Criteria*

And excluding individuals meeting any of the following:

- Received both the device of interest (ThermoCool STSF) and the comparator device (ThermoCool ST)
- Underwent an intracardiac catheter ablation prior to the index procedure
- Had a surgical cardiac ablation any time prior to or at the same time as the index procedure
- Had a prior heart transplant or long-term heart assist system implantation prior to the index procedure
- Patients with less than 7 days of follow-up due to administrative censoring*

* This censoring event will be present if the latest date of follow-up - date of index procedure < 7 days. The latest date of follow-up is determined by the date that the data is extracted from the EHR.

VT patients will be identified by combining intracardiac catheter ablation procedure codes of VT ablation (CPT Codes: 93654, ICD-10-PCS codes: 025K3ZZ, 025L3ZZ, 025M3ZZ) with ICD-10-CM diagnosis code of VT (I47.2) or ICD-9-CM diagnosis code of VT (427.1) associated with the same intracardiac catheter ablation procedure encounter.

An evaluation of the performance of this algorithm to identify VT patients from the EHR system was conducted at Mercy and Mayo Clinic through a manual chart review process by cardiac electrophysiologists in a random sample of non-study population patients in this NESTcc test-case study and obtained high PPVs for a diagnosis of VT either in a primary or secondary position (90% at Mercy and 100% at Mayo Clinic).

A prior diagnosis of MI recorded in the database before the index procedure will determine which patients in the VT population had cardiac ablation for ischemic VT. Patients who had VT ablation and did not have a prior diagnosis of MI in the database will also be included as a sensitivity analysis (ie, exploratory analysis of overall VT).

For the persistent AF population, a sensitivity analysis will be conducted among those who had at least one prescription of class I or III AAD prior to the index procedure.

For the ischemic VT population, a sensitivity analysis will be performed to exclude patients with a history of non-ischemic cardiomyopathy.

## 5.3 Primary Independent Variable(s)

### Persistent AF Population:

- Device of interest: ThermoCool ST catheter
- Comparator device: ThermoCool STSF catheter

### VT Population:

- Device of interest: ThermoCool STSF catheter
- Comparator device: ThermoCool ST catheter

## 5.4 Subgroup/Stratification Variable(s)

## Persistent AF Population:

- A prior prescription of class I or III AAD before the index procedure recorded in the database

## Ischemic VT Population:

- A history of non-ischemic cardiomyopathy

### 5.5 Covariates

An extensive list of covariates is considered for persistent AF (**Table 3a**). A reduced set of covariates is considered for VT (**Table 3b**) given sample size considerations.

**Table 3a.** Covariates for Persistent AF Population

**Demographic Information**
- Patient age
- Patient sex
- Race

**Hospital and provider characteristics**
- Hospital bed size
- Operator experience (defined as the number of AF ablation procedures performed by cardiac electrophysiologists during the 12 months prior to the index procedure)

**Medical history, arrhythmia related information and clinical characteristics**
- Calendar year of procedure
- History of valve replacement
- Mitral valve stenosis
- Percutaneous coronary intervention
- Coronary artery bypass grafting
- Body mass index*
- Anemia
- Hypertension
- Diabetes mellitus (both type 1 and type 2)
- Obstructive sleep apnea
- Vascular disease history (prior MI or peripheral arterial disease or aortic plaque)
- Congestive heart failure
- Chronic pulmonary disease
- Ischemic stroke or hemorrhagic stroke or transient ischemic attack or thromboembolism
- Implantable cardioverter defibrillator or pacemaker
- Hospitalizations: AF related
- Chronic renal disease
- Elixhauser comorbidity index
- Electrical cardioversion (direct current cardioversion) for AF
- History of supraventricular arrhythmia
- History of ventricular arrhythmia

**Medications**
- Use of class I or III antiarrhythmic drugs
- Use of class II or IV antiarrhythmic drugs (beta blocker, calcium channel blocker)
- Use of anticoagulants
- Use of antiplatelets

**Table 3b.** Covariates for VT Population

**Demographic Information**
- Patient age
- Patient sex
- Race

**Hospital and provider characteristics**
- Operator experience (defined as the number of VT ablation procedures performed by cardiac electrophysiologists during the 12 months prior to the index procedure)

**Medical history, arrhythmia related information and clinical characteristics**
- Calendar year of procedure
- History of valve replacement
- Body mass index*
- Anemia
- Hypertension
- Diabetes mellitus (both type 1 and type 2)
- Congestive heart failure
- Ischemic stroke or hemorrhagic stroke or transient ischemic attack or thromboembolism
- Implantable cardioverter defibrillator or pacemaker
- Hospitalizations: VT related
- Elixhauser comorbidity index
- History of AF

**Medications**
- Use of class I or III antiarrhythmic drugs
- Use of anticoagulants

* Recorded body mass index or calculated body mass index based on weight and height (weight in kg/height in $m^2$), the latest measurement prior to the index ablation procedure. Note: Demographic information, procedural characteristics, hospital and provider characteristics are recorded at the time of the index procedure. Medications are based on 6 months prior to the index procedure. Medical history, arrhythmia-related information and clinical characteristics use all available information prior to the index procedure unless otherwise specified.

## 5.6 Study Outcome(s)

- ### Primary Safety Outcomes

### 5.6..1. Persistent AF Population:

The primary safety endpoint for persistent AF is similar to the PRECEPT Trial, the IDE clinical study that was conducted for a label expansion for ThermoCool STSF for persistent AF [9]. The safety endpoint is the cumulative incidence of a composite of primary adverse events (PAEs) of the initial ablation procedures using the study catheter. The majority of PAEs included in the composite endpoint are measured from the time of the index ablation procedure until 7 days of the index procedure. However, one adverse event is included if it occurs within 30 days and two others within 90 days after the index ablation procedure to allow for events that may take some time to become clinically overt and diagnosed to occur. The list of PAEs included in the composite endpoints consists of the following:

Within 7 days of the index ablation:
- Death
- Acute MI
- Acute stroke/cerebrovascular accident
- Transient ischemic attack (TIA)
- Thromboembolism
- Heart block
- Pericarditis

- Diaphragmatic paralysis
- Pneumothorax
- Pulmonary edema
- Major vascular access complication or bleeding requiring transfusion

Within 30 days of the index procedure:
- Cardiac tamponade/perforation

Within 90 days of the index procedure:
- Pulmonary vein stenosis
- Atrioesophageal fistulas

### 5.6..2. **VT Population:**

The primary safety endpoint for VT is similar to that used in the Post-Approval THERMOCOOL VT (NaviStar ThermoCool Catheter for Endocardial RF Ablation in Patients With Ventricular Tachycardia) Trial [16]. The primary safety endpoint consists of the cumulative incidence of a composite of cardiovascular-specific adverse events (CSAE) during and within 7 days post-ablation, including:
- Death
- Acute MI
- Acute stroke
- Deep venous thrombosis
- Pulmonary embolus
- Complete heart block
- Pericardial effusion with hemodynamic compromise
- Cardiac perforation
- New acute severe mitral or aortic regurgitation
- Arterial dissection
- Vascular injury

The three methods for detecting events during the post-ablation safety event evaluation period in this study include: 1) identification using diagnosis and procedure codes/algorithms for primary safety events listed above (eg, pericarditis) that may not be detected by the other 2 criteria below (#2 and #3); 2) hospitalization/readmission or emergency department visit during the safety event identification period of 7-day period, regardless of diagnosis; and 3) length of stay ≥ 48 hours after the index ablation, regardless of diagnosis. Once detected by one of these three methods, the events will be verified through manual chart reviews by a very experienced cardiac electrophysiologist at Mercy, and another at Mayo Clinic using a standardized set of criteria (Appendix 6 provides more detail). Cardiac electrophysiologists will not review the charts of their patients for whom they performed the ablation to determine if they had a safety event; chart review of the electrophysiologist's patients will be conducted by a second electrophysiologist.

## • Exploratory Real-World Effectiveness Outcomes

### 5.6..1. **Persistent AF Population:**

The exploratory effectiveness endpoint for persistent AF is the cumulative incidence of a composite endpoint at 6 months and 1 year after the index procedure of
- Rehospitalization for atrial tachyarrhythmia (including AF, atrial tachycardia [AT], and atypical atrial flutter [AFL])
- Rehospitalization for heart failure
- Electrical cardioversion for AF/AT/AFL
- Repeat ablation for AF/AT/AFL

Consistent with treatment guidelines [17] and past approaches [18], a 3-month blanking period (during which healing and stabilization occur) for persistent AF will be implemented for the assessment of effectiveness outcomes across groups.

### 5.6..2. **VT Population:**

The exploratory effectiveness endpoint for VT is the cumulative incidence of a composite endpoint at 6 months and 1 year after the index procedure of

- Rehospitalization for VT
- Rehospitalization for heart failure
- Repeat ablation for VT

**Table 4.** Proposed primary safety and exploratory effectiveness outcomes for persistent AF and VT

| Outcome | Persistent AF Population | VT Population |
|---|---|---|
| **Safety** | **Within 7 days after procedure** | **Within 7 days after procedure** |
| | • Death | • Death |
| | | • Pericardial effusion with hemodynamic compromise |
| | | • Cardiac perforation |
| | • Acute MI | • Acute MI |
| | • Acute stroke/cerebrovascular accident | • Acute stroke |
| | • Transient ischemic attack (TIA) | |
| | • Heart block | |
| | | • Complete heart block |
| | • Pericarditis | |
| | • Thromboembolism | • Deep venous thrombosis<br>• Pulmonary embolus |
| | • Diaphragmatic paralysis | |
| | • Pneumothorax | |
| | • Pulmonary edema | |
| | • Major vascular access complication or bleeding requiring transfusion | |
| | | • New acute severe mitral or aortic regurgitation |
| | | • Arterial dissection |
| | | • Vascular injury |
| | **Within 30 days after ablation:**<br>• Cardiac tamponade/perforation | |
| | **Within 3 months after ablation**<br>• Pulmonary vein stenosis<br>• Atrio-esophageal fistulas | |
| **Effectiveness** | **During 6 months and 1 year of follow-up after procedure after a 3-month blanking period** | **During 6 months and 1 year of follow-up after procedure (no blanking period)** |
| | • Rehospitalization for AF/AT/AFL | |
| | | • Rehospitalization for VT |
| | • Rehospitalization for heart failure | • Rehospitalization for heart failure |
| | • Repeat ablation for AF/AT/AFL | |
| | | • Repeat ablation for VT |
| | • Electrical cardioversion for AF/AT/AFL | |

Since the primary objective of this study is to evaluate the safety of the devices for the new indications being sought, the follow up rate at 7 days after the index ablation is most relevant for VT and 11 of 14 persistent AF safety events. Both Mercy and Mayo Clinic had excellent follow-up rates at 7 days (98% at Mercy and >99% at Mayo Clinic). For persistent AF, the follow up rates at 30 days (for cardiac tamponade/perforation) and 3 months (for pulmonary vein stenosis and atrio-esophageal fistulas) after the index ablation are also most relevant. Mercy and Mayo Clinic also had excellent follow-up rates at 30 days and 3 months (see section 5.1).

# 6 Statistical Analysis

## 6.1 Propensity Score Strategy

**Prior to the outcome analysis**, the 2-stage propensity score strategy will be used within each patient population separately within each health system to reduce confounding in the comparison of outcomes between groups. The methodology will be applied separately within Mercy and Mayo Clinic since this study will use a distributed data network approach where each healthcare system analyzes their own data separately using common methods and treatment effect estimates are pooled subsequently.

- ### Stage 1: Building the Propensity Score Model

The propensity score model will be developed within each patient population separately using catheter group as the outcome and potential confounders as covariates (see **Table 3a and Table 3b** for a list of covariates) in a multivariable logistic regression model for each patient population separately within each health system to generate the propensity score for each patient. The propensity score represents the probability that the patient was in the device group of interest (ThermoCool ST for persistent AF and ThermoCool STSF for ischemic VT).

An independent statistician with no access to the study outcome data will be identified to build the propensity score model using the propensity score methods described below for each patient population separately within each health system to generate propensity score models to remove the potential for bias in the analysis.

- ### Stage 2: Selecting a Covariate Balancing Method

For persistent AF, the propensity score method using propensity score weighting (average treatment effect on the treated weights) [19] will be used. Patient weights in the comparator group will be trimmed/winsorized at the 95th percentile of the weight distribution (ie, all weights with value above the 95th percentile are set equal to the 95th percentile weight).[20]

The propensity score methods that are considered for creating covariate balance between the test catheter group and the comparator catheter group include: 1) the stratification on the propensity score using 5 strata based on quantiles of the propensity score distribution [21-23] and 2) the weighting methods of the average treatment effect on the treated, where the treated subjects receive a weight of 1 and the untreated subjects receive a weight based on the odds, $\frac{e_i}{1-e_i}$, where $e_i$=propensity score, without [19] and with [20] trimming. The approach starts with the propensity score stratification method to create covariate balance. If the propensity score stratification method does not reach good covariate balance, then the propensity score weighting methods is considered. If the balance of covariates achieved using the weighting method is better than the stratification method, then the weighting method is selected. Evaluations of balance are based on the number of covariates with an absolute standardized difference having a value of ≤0.20, a criterion used for establishing covariate balance in the literature [24]. An absolute standardized difference ≤0.20 for all variables is considered to be good balance. The method that results in the fewest number of covariates having an absolute standardized difference value >0.20 is selected. If the two methods tie in the number of covariates with absolute standardized difference value >0.20, then the method with the smallest average absolute standardized difference across all variables is selected (ie, the absolute standardized difference value of all covariates in the propensity score model is averaged and the selection of the method is made depending on which method provides the lowest average absolute standardized difference value).

For the VT analysis, we propose the use of a single arm design to compare the cumulative incidence of a composite

safety endpoint to a performance goal[11] among patients with ischemic VT who had a procedure performed with the ThermoCool STSF catheter (pooled across Mercy and Mayo Clinic) for hypothesis testing in consideration of the relatively small sample size, inadequate covariate balance achieved with propensity score approaches, and the possibility of zero events in one or more catheter groups due to the small sample size in the ischemic VT populations in the Mercy and Mayo Clinic databases. A single arm design using a performance goal approach is also consistent with the approach proposed by a recent publication by FDA authors when proper control data are not available [11].

For the VT analysis, we also propose an exploratory analysis comparing the ThermoCool STSF group and the ST group using the propensity score weighting approach with comparator group patients' weights trimmed (ie, winsorized) at the 95th percentile of the weight distribution (ie, all weights with value above the 95th percentile are set equal to the 95th percentile weight).[20]

## 6.2 Descriptive Reporting of Baseline Characteristics

Demographic, clinical, procedural, and hospital and provider characteristics at baseline will be summarized descriptively for each group. Standard descriptive summaries for continuous variables will include the number of subjects with data, mean, and standard deviation. The count and percentage will be generated for categorical variables.

## 6.3 Outcome Analysis of Primary Safety Endpoint(s)

As described above, a head-to-head comparison using a non-inferiority design with a pre-specified non-inferiority margin will be conducted for a composite safety endpoint for persistent AF and a single arm design using a performance goal will be conducted for a composite safety endpoint for ischemic VT.

### 6.3..1. Persistent AF Population:

Evaluations of non-inferiority with respect to safety will be based on the absolute risk (ie, risk difference) at 3 months using data balanced on pre-specified measured covariates. Given the longer evaluation period of the outcome, survival analysis methods will be used to estimate the risk difference.

This section describes survival methods using a weighted propensity score approach to balancing the covariates in the data. First, the propensity score will be calculated for each patient. Patients in the subject device group will receive a weight of 1, therefore the estimate of survival is the conventional Kaplan Meier estimator, and those in the comparator device group will receive a weight not equal to 1, therefore a weighted Kaplan Meier estimator will be used to calculate survival [25]. The risk difference between the subject device group (s) and the comparator device group (c) is represented as $\hat{\Delta}= \widehat{CI}_s - \widehat{CI}_c$, where $\widehat{CI}_s = 1 - \hat{S}(90)$, $\widehat{CI}_c$= 1- $\hat{S}^w(90)$, with $\hat{S}(90)$ denoting the Kaplan Meier estimate of survival and $\hat{S}^w(90)$ the weighted Kaplan Meier estimate of survival at 90 days. The variance of the difference is calculated as $\widehat{var}(\hat{\Delta}) = \widehat{\text{var}}\left(\widehat{CI}_s\right) + \widehat{\text{var}}\left(\widehat{CI}_c\right)$, where $\widehat{\text{var}}\left(\widehat{CI}_s\right)$=$\widehat{var}\left(\hat{S}(90)\right)$ and $\widehat{\text{var}}\left(\widehat{CI}_c\right)$=$\widehat{var}\left(\hat{S}^w(90)\right)$. Estimation of the variance corresponding to the survival estimates in the subject device group, $\widehat{\text{var}}\left(\widehat{CI}_s\right)$, will be based on a conventional greenwood estimate because all patients receive a weight of 1. Estimation of the variance corresponding to the survival estimates in the comparator device group, $\widehat{\text{var}}\left(\widehat{CI}_c\right)$, will be based on an infinitesimal jackknife because patients do not receive the same weight of 1. The two-sided 90% Wald confidence interval for the difference is: $\hat{\Delta} \pm Z_{1-0.05} * \widehat{SE}_{\hat{\Delta}}$, where $\widehat{SE}_{\hat{\Delta}} = \sqrt{\widehat{\text{var}}\ (\hat{\Delta})}$. The two-sided 90% Wald confidence interval within each catheter group is: $\widehat{CI} \pm Z_{1-0.05} * \widehat{SE}_{\widehat{CI}}$, where $\widehat{SE}_{\widehat{CI}} = \sqrt{\widehat{\text{var}}\ (\widehat{CI})}$. All confidence intervals described in this section are for descriptive reporting of results, not hypothesis testing.

### 6.3..2. Ischemic VT Population:

The safety outcome analysis among ischemic VT patients will be based on an estimate of a simple proportion at 7 days, $\hat{p} = \frac{\#\, safety\ events}{\#\, patients}$ given the shorter evaluation period of the outcome. For hypothesis testing, $\#\ patients$ is the total number of patients in the ThermoCool STSF catheter group combined in Mercy and Mayo data and $\#\ safety\ events$ is the number of patients who had a composite safety event in the ThermoCool STSF catheter group combined in Mercy and Mayo data. For proportions calculated for an individual catheter group within a data source, a descriptive summary

of the data, $\# \, patients$ is the number of patients in the catheter group and $\# \, safety \ events$ is the number of patients who had a composite safety event in the catheter group. Confidence intervals (two-sided 90%) and one-sided p-values are based on the Clopper-Pearson exact method.

### 6.3..3. Combining Effect Estimates Across Data Sources:

Analyses of the risk difference will be performed separately in Mercy and Mayo Clinic data sets. Study outcomes will be obtained through standard queries to each data set and combined using a distributed analytics approach similar to the Sentinel Initiative, which can decrease the risk of disclosing sensitive information in multicenter studies and allows each healthcare system to maintain their patient electronic health record data within their organization. Data will be standardized in the Observational Medical Outcomes Partnership (OMOP) common data model to facilitate common analyses in two data systems.

A fixed-effect model, in which a common effect is assumed across data sources, will be used to combine effect estimates (ie, risk differences) from Mercy and Mayo Clinic. A fixed-effect model (vs. a random-effects model) is chosen based on several considerations as highlighted in a scientific statement from the American Heart Association: "The choice of a fixed-effect model should be based on 2 important factors: whether the included studies are functionally identical, meaning they include similar or nearly identical populations, interventions, and methods, and whether the goal of synthesis of results across studies is to compute a common effect size that is applicable to populations similar or identical to those included but not generalizable to other populations" [26]. The types of inferences desired in this context are more consistent with a fixed-effect model since inferences apply to "this collection of studies and say nothing about other studies that may be done later, could have been done earlier, or may have already been done…" [27]. The argument about the nature of inferences is independent of one about effect heterogeneity.

In addition, an argument for a fixed-effect model based on low heterogeneity can be made in this application based on the harmonized approach to study design, in which the inclusion/exclusion criteria, treatment groups, covariates and outcome measurement are the same (or approximately so) across the data sources. A fixed-effect model is also more compelling for the relatively small number of studies since alternatives can result in extremely wide confidence intervals in order to obtain reasonable coverage [28,29].

The risk differences from Mercy and Mayo Clinic will be combined using a fixed-effect model (ie, the inverse-variance method) to generate the overall risk difference with the corresponding confidence interval. In the inverse-variance method, the weight given to each study site is equal to the inverse of the variance of the risk difference (ie, 1 over the square of its standard error). All other things equal, a study site with the larger sample size (which has a smaller standard error) will be given more weight than the study site with fewer patients (which has a larger standard error). Calculation of the average treatment effect from a fixed-effect model is straightforward [30]. For each data source ($q = 1, 2$), we estimate the risk difference, $\hat{\Delta}_q$. The variance of this estimate is denoted by $\widehat{\text{var}}(\hat{\Delta}_q)$ and a weight is constructed by taking the inverse of this quantity, $w_q = \frac{1}{\widehat{\text{var}}(\hat{\Delta}_q)}$. The average treatment effect across studies is then estimated using a weighted mean, $\bar{\Delta} = \frac{\sum_{q=1}^{2} w_q \hat{\Delta}_q}{\sum_{q=1}^{2} w_q}$. The variance of this weighted mean is then $\widehat{\text{var}}(\bar{\Delta}) = \frac{1}{\sum_{q=1}^{2} w_q}$ and the standard error is $\widehat{SE}(\bar{\Delta}) = \sqrt{\widehat{\text{var}}(\bar{\Delta})}$. Two-sided Wald confidence intervals (90%) can be calculated in the conventional way: $\bar{\Delta} \pm Z_{1-0.05} * \widehat{SE}_{\bar{\Delta}}$. This is the only confidence interval used for hypothesis testing for the persistent AF population.

### 6.3..4. Hypothesis testing:

For persistent AF, the average risk difference for hypothesis testing is the difference in the cumulative incidence (CI) between the two treatment arms, averaged across the two data sources. The average risk difference is represented as $\bar{\Delta}$. As discussed below in Section 6.5., the non-inferiority margin for the risk difference is assumed to be $\delta = 0.07$ for persistent AF, corresponding to the anticipated cumulative incidence in the ThermoCool STSF group.

For persistent AF, the following null ($H_{01}$) and alternative ($H_{a1}$) hypotheses are considered:

$H_{01}: \bar{\Delta} \geq \delta$
$H_{a1}: \bar{\Delta} < \delta$

The hypothesis test will be based on the upper bound of a two-sided Wald 90% confidence interval for the average risk difference across data sources, $\widehat{\bar{\Delta}} \pm Z_{1-0.05} * \widehat{SE}_{\widehat{\bar{\Delta}}}$. Therefore, the hypothesis test will be based on a one-sided 5% significance level. A one-sided P-value is calculated as $\Phi(Z), where\ \Phi$ is the cumulative distribution function for a standard normal distribution and $Z = \frac{\widehat{\bar{\Delta}}-\delta}{\widehat{SE}_{\widehat{\bar{\Delta}}}}$. If the upper bound of the two-sided Wald 90% confidence interval for the average risk difference across data sources is less than the designated non-inferiority margin, then there is evidence supporting a conclusion of non-inferiority.

For ischemic VT, the cumulative incidence is represented by $p$. The performance goal, $PG$, is set to $0.15$, corresponding to twice the anticipated cumulative incidence in the ThermoCool ST group. The following null ($H_{02}$) and alternative ($H_{a2}$) hypotheses are considered:

$H_{02}: p \geq PG$
$H_{a2}: p < PG$

The hypothesis test will be based on the upper bound of a two-sided Clopper-Pearson exact 90% confidence interval for $\hat{p}$. Therefore, the hypothesis test will be based on a one-sided 5% significance level. A one-sided Clopper-Pearson exact P-value will also be reported. If the upper bound of the two-sided Clopper-Pearson exact 90% confidence interval for the cumulative incidence of a composite safety endpoint in the ThermoCool STSF catheter group combined in Mercy and Mayo data is less than the performance goal of 15%, then the result is statistically significant.

### 6.4 Analysis of Exploratory Endpoint(s)

As stated above, no hypothesis testing will be performed for the exploratory endpoints. Point estimates for the cumulative incidence and their confidence intervals within each group and for the risk difference between the groups within each dataset will be provided, based on the methods for point and variance estimation described above.

We will conduct a descriptive analysis to evaluate patients' characteristics with and without at least one-year in-person follow-up data for the exploratory effectiveness evaluation to assess any potential selection bias.

A detailed SAP accompanies this protocol.

### 6.5 Sample Size and Power Calculation

- **Estimated Number of Patients**

Based on a review of the EHR and other electronic databases of Mercy and Mayo Clinic, the numbers of patients who underwent an intracardiac catheter ablation of persistent AF and VT with ThermoCool catheters from Mercy and Mayo Clinic are shown in Table 5. There were more patients ablated with ThermoCool ST for persistent AF than were ablated with ThermoCool STSF for ischemic VT. There were more patients in the comparator groups than the study test groups for persistent AF at Mercy and for ischemic VT at Mayo Clinic.

**Table 5.** The estimated number of patients who underwent an intracardiac catheter ablation of persistent AF and VT with ThermoCool catheters from Mercy and Mayo Clinic from January 2014 to April 2021

| | STSF (comparator) | ST (test) |
|---|---|---|
| **Persistent AF** | | |
| Mercy | 763 | 186 |
| Mayo Clinic | 164 | 333 |
| **Total** | 927 | 523 |

| | STSF (test) | ST (comparator) |
|---|---|---|
| **Overall VT population** | | |
| Mercy | 51 | 79 |
| Mayo Clinic | 98 | 412 |
| **Total** | 149 | 491 |
| **Ischemic VT** | | |
| Mercy | 35 | 23 |
| Mayo Clinic | 35 | 84 |
| **Total** | 70 | 107 |
| **Non-ischemic VT** | | |
| Mercy | 16 | 56 |
| Mayo Clinic | 63 | 328 |
| **Total** | 79 | 384 |

- ## Expected Event Rate

### 6.5..1. Persistent AF Population

The expected event rate of complications among patients undergoing cardiac ablation for persistent AF in the U.S. is estimated to be approximately 7% in real-world settings with diverse patients and operators based on the following:

1) In the PRECEPT IDE study of persistent AF ablation with the ThermoCool STSF catheter (the comparator device of this study) [9], the observed primary safety endpoint rate was 4.1% (15 events in 14 participants/348 patients) with the 1-sided exact 97.5% upper confidence bound of 6.7%. This was significantly lower than the specified performance goal of 16.0%. However, the PRECEPT study is a well-controlled and stringently monitored study and is not representative of real-world practice in the Mercy and Mayo healthcare systems because:

- PRECEPT specifically excluded subjects with pre-existing medical history/conditions, such as patients with left atrial (LA) size ≥50mm, left ventricular ejection fraction (LVEF) <40%, or New York Heart Association (NYHA) functional class III/IV. These exclusions were designed to reduce the risks of adverse clinical outcomes of the ablation procedure, such as the risk of cardiovascular hospitalization and the risk of adverse events. Data from PRECEPT and other well controlled clinical studies also come from sites that are selected from research centers of excellence. These sites are generally high volume and operators are selected because they are known experts in their field and are very experienced in AF ablation. The latest Heart Rhythm Society (HRS) consensus statement [31] noted specifically that the complication rate of AF ablation will be higher than that described by controlled studies when more diverse sites with lower procedural volume and less experienced cardiac electrophysiologists are included, as in current real-world practice. The more diverse and heterogenous patient population in RWD studies is likely to have a wider range of comorbidities and more variable adherence to anticoagulation medications than carefully controlled clinical study populations [32,33]. Therefore, the selected patient and cardiac electrophysiologist population included in clinical studies is likely to have a lower rate of complications than the more diverse patient and cardiac electrophysiologist population in the real-world setting.

2) Publications of RWD studies support that complication rates of AF ablation in real-world settings are higher than that in a controlled study such as PRECEPT. In-hospital estimates from 3 published RWD studies of complication rates after AF ablation in the U.S. are shown in **Table 6**. Since the source data from these 3 RWD studies are limited to in-hospital complications, they may underestimate the rates that include post-procedural complications. The rate of real-world complications after persistent AF ablation is likely to be closer to the 95% confidence interval upper bound of the safety event rate observed in PRECEPT study (~7%). The published RWD studies are:

- An RWD study using the nationally representative U.S. National Inpatient Sample database, including 39,562 AF catheter ablation procedures (representing 190,398 AF catheter ablation procedures in the U.S.) performed between 2000 and 2013, reported a mean in-hospital complication rate of 7.2% after AF ablation. The study also reported that lower hospital volumes were associated with higher complication rates [34].

- A separate analysis of the U.S. National Inpatient Sample database between 2000 and 2010 also found that the procedures were mostly performed by low-volume operators, and lower annual operator and hospital volumes were associated with higher complication rates [35].
- An RWD study using the U.S. Vizient Health Systems database, a large hospital database reported the in-hospital complication rate after AF ablations with the ThermoCool ST or STSF catheter ranged from 10.1% at low-volume sites to 5.3% at high-volume sites. The mean in-hospital complication rate was 6.3% after persistent AF ablation [36].

3) The HRS consensus statement recognized that persistent AF patients with additional comorbidities (e.g., low ejection fraction [EF]) experienced higher rate of complications from catheter ablation (~15% [see Table 7 in Calkin et al. 2017 [31]]); the panel nonetheless considers catheter ablation safe and effective in these higher risk patients.
4) This NESTcc test case study using RWD has minimal patient exclusion criteria and may therefore include patients with more severe disease or comorbidities than those included in clinical studies. Mercy and Mayo Clinic EHR system databases are generally representative of the U.S. population of persistent AF patients who had a cardiac ablation procedure (see **Table 2a**). This study does not exclude any sites from Mercy and Mayo Clinic based on site volume or operators' experience. Therefore, a more diverse group of sites and operators (low and high volume, more or less experience) than the clinical trial population will be included leading to higher complication rates as noted by the HRS consensus statement.

For these reasons, we assume a safety event rate closer to the upper bound of 95% confidence interval of PRECEPT safety event rate of 7%. We also assume a 7% region of indifference (non-inferiority margin). This is equivalent to a performance goal of 14%, which is 2 percentage points lower than the performance goal of the PRECEPT clinical study [9], and will show a safety profile within the margin of recently approved catheters for the treatment of persistent AF [9,37].

The 7% non-inferiority margin represents the threshold for acceptance of the upper bound of the two-sided Wald 90% confidence interval (corresponding to a one-sided 95% confidence interval) of the pooled risk difference of the primary safety endpoint between the subject device group and the comparator device group. If the upper bound of the two-sided Wald 90% confidence interval (corresponding to a one-sided 95% confidence interval) of the pooled risk difference of the primary safety endpoint between the treatment and comparator groups is less than the non-inferiority margin of 7%, then there is evidence supporting a conclusion of non-inferiority. Given the scenario of a sample size of 165 per the study group (ie, the minimum required sample size for 80% power for persistent AF [see Table 7 below]) and the complication rate is 7% in the comparator group, a complication rate of 8% in the treatment group would be considered non-inferior while a complication rate of 9% would be rejected as inferior. In term of the number of cases, the complication rate of 7% would be 12 cases that meet the primary endpoint definition out of the 165 study subjects, and the complication rate of 9% would be 15 cases. Therefore, if the number of cases increased from 12 to 15 out of the 165 subjects, the treatment catheter would be considered inferior to the comparator catheter.

**Table 6.** Complication rates of AF ablation from RWD studies in the U.S.

| **Reference** | **RWD source** | **# patients/ procedures** | **Population** | **Complication rate** | **Complication definition** |
|---|---|---|---|---|---|
| Hosseini 2017 [34] | U.S. National Inpatient Sample (2000-2013) | Representing 190,398 AF procedures in the U.S. | AF | 7.2% | In-hospital complications:<br>- Cardiac (post-operative cardiac block, MI)<br>- Pericardial (tamponade, hemopericardium, pericarditis, and pericardiocentesis)<br>- Vascular (arteriovenous fistula, blood vessel injury, accidental puncture, injury to the retroperitoneum, vascular complications requiring surgery, and other iatrogenic vascular complications)<br>- Post-operative hemorrhage or hematoma (including post-operative hemorrhage requiring blood transfusion) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | - Postoperative stroke or TIA<br>- Pneumothorax or hemothorax<br>- Diaphragm paralysis<br>- Infections (fever, septicemia, and postprocedural aspiration pneumonia)<br>- In-hospital deaths |
| Deshmukh 2013 [35] | U.S. National Inpatient Sample (2000-2010) | Representing 93,801 AF procedures in the U.S. | AF | 6.3% | In-hospital complications:<br>- Cardiac (iatrogenic cardiac complications, pericardial complications, and acute MI)<br>- Pulmonary (pneumothorax, postoperative respiratory failure, and iatrogenic complications)<br>- Neurological (stroke and TIA)<br>- Vascular access (postoperative hemorrhage, postoperative hemorrhage requiring blood transfusion, and vascular complication requiring surgical repair)<br>- Postoperative infection<br>- In-hospital death |
| Natale 2020 [36] | U.S. Vizient Health Systems | 192 | Persistent AF | 6.3% | In-hospital complications:<br>- Cardiac (tamponade and other pericardial events, and MI)<br>- Respiratory<br>- Pulmonary embolism<br>- Stroke, cerebral or pre-cerebral occlusion/stenosis without infarction<br>- Phrenic nerve injury<br>- Vascular access<br>- Hemorrhage and/or blood transfusion |

### 6.5..2. VT Population

Three published meta-analysis studies have reported summary complication rates of VT catheter ablation between **7.1%-9.4%** in RWD studies [38-40].

The meta-analysis by Pothineni et al. [39] which included two real-world database studies of VT ablation with a total of 14,352 procedures and 18 clinical studies (3 randomized and 15 non-randomized studies) with a total of 1,705 procedures, found higher complication rates in RWD studies than in clinical studies (**9.39% vs. 7.97%,** p = 0.06), particularly cardiac/pericardial (4.47% vs. 2.29%, p < 0.0001) and vascular access complications (6.9% vs. 3.0%; p <0.0001) (See **Figure 1**).

The study by Palaniswamy et al. [41], one of the RWD studies included in the Pothineni et al. meta-analysis using the nationally representative U.S. National Inpatient Sample database between 2002 and 2011, reported an overall rate of any in-hospital complication of **11.2%** (vascular: 6.9%; cardiac: 4.3%; neurologic: 0.5%) and an in-hospital mortality of 1.6% among patients aged at least 18 years of age with a primary diagnosis of VT and a secondary diagnosis of prior MI.

Another RWD study by Cheung et al. [42] using the nationally representative U.S. Nationwide Readmissions Database evaluated 4,109 admissions for catheter ablation of MI-associated VT occurring between 2010 and 2015 and reported similar index admission in-hospital complication rate and mortality rate after VT ablation of **11.5%** and 2.7%, respectively [42].

A recent meta-analysis by Ding et al. [40] that included 50 studies (45 cohort studies, 4 RCTs and 1 case-control study) with a total of 3,833 patients undergoing 4,319 VT ablation procedures reported an overall complication rate of **9.4%** (95% CI,

8.1–10.7) in ischemic cardiomyopathy populations and **7.1%** (95% CI, 6.0–8.3) in non-ischemic cardiomyopathy populations.

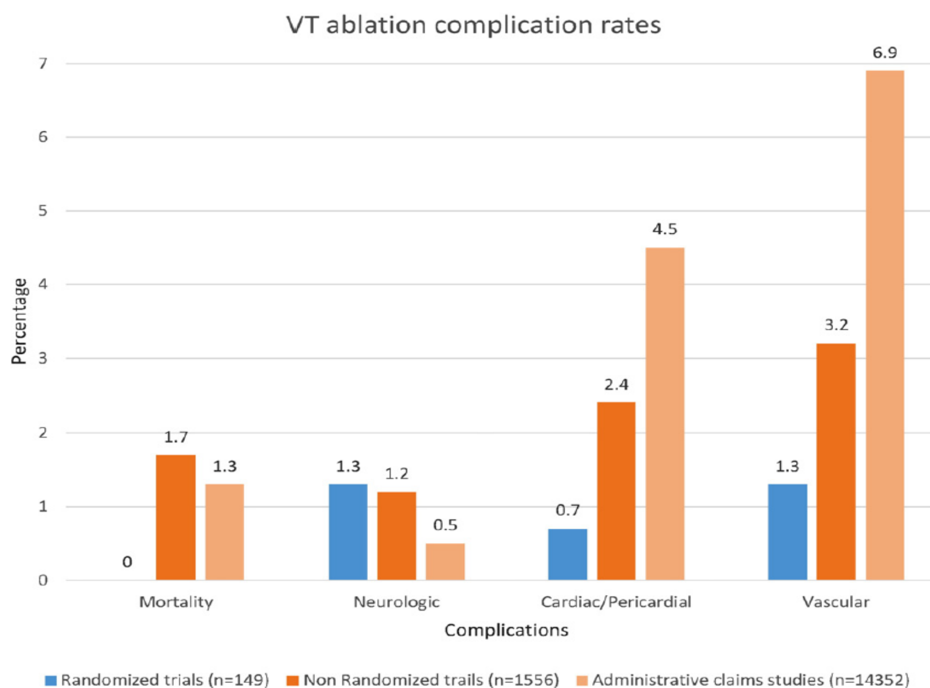


**Fig. 1.** Comparison of pooled complications of ventricular tachycardia ablation per 100 procedures.

As described above, this NESTcc test case study has minimal patient exclusion criteria and no exclusion based on site volume or operators' experience of any sites from the Mercy and Mayo Clinic healthcare systems. Mercy and Mayo Clinic EHR system databases are generally representative of the U.S. population of VT patients who had a cardiac ablation procedure (see **Table 2b**). Given the in-hospital complication rate after VT ablation in patients with a prior MI of **11.2%** in the Palaniswamy et al. [41] and **9.4%** in ischemic cardiomyopathy populations in the Ding et al. [40] meta-analysis the expected complication event rate after VT ablation among patients with prior MI is expected to be approximately 7.5%-9.5%. In the absence of a clear rule for a clinically important difference in complication rate, we assume a 7.5% non-inferiority margin that is equal in size to the 7.5% of the expected complication rate, following the approach that has been used for label extensions of cryoballoon and ThermoCool STSF catheters for persistent AF using IDE clinical studies.

- ## Sample Size Estimation

Sample size estimation is based on statistical power for the primary objectives (ie, safety analyses) proposed in this study. The minimum required sample size was calculated separately for the planned hypothesis tests of the primary composite safety endpoints in the persistent AF and ischemic VT populations.

For persistent AF, the hypothesis test will be based on two-group comparison data pooled across data sources using the upper bound of the two-sided Wald 90% confidence interval (corresponding to a one-sided test at the 0.05 alpha-level). Therefore, power calculations used a two-sample test for a difference in proportions based on a Pearson chi-square test as implemented in PROC POWER in SAS, version 9.4. For persistent AF, we assume the composite safety endpoint proportion is 0.07 in both study groups (ie, an assumed population difference in proportions of 0), a non-inferiority margin of 0.07, and a one-sided test at the 0.05 alpha-level to determine the minimal sample size that provided more than 80% power; this sample size was 330 across both study groups (or 165 per group) (Table 7).

**Table 7. Sample Size Estimates for Achieving 80% Power for a Composite of Primary Safety Events**

| Event rate in the comparator group | Event rate in the device of interest group | Non-inferiority margin between 2 groups in event rates | Sample size per treatment group for 80% power with α=0.05 (one-sided) | | |
|---|---|---|---|---|---|
| | | | Follow-up rate | | |
| | | | No loss of follow-up | 95% | 91% |
| Persistent AF Population | | | | | |
| 7% | 7% | 7% | 165 | 174 | 181 |

For ischemic VT, the hypothesis test will be based on a single group (ThermoCool STSF) with data pooled across the two data sources using the upper bound of the two-sided 90% confidence interval for a one-sample exact test of a proportion. Therefore, power calculations used a one-sample exact test for a proportion as implemented in PROC POWER in SAS, version 9.4. For ischemic VT, we assume the composite safety endpoint proportion is 0.075, a performance goal of 0.15, and a one-sided test at the 0.05 alpha-level. Given the sample size of 70 (Table 5), the estimated power is 57%.

Based on the patient counts up to April 2021 (see Table 5), statistical power is expected to be adequate for persistent AF. However, sample size for ischemic VT is currently under-powered using only Mercy and Mayo Clinic EHR databases.

Due to the low statistical power (57%) for the ischemic VT hypothesis test in this study, we propose to supplement the NEST test case with an additional data source, a comparative study (ThermoCool STSF vs. ST) in the Premier Healthcare Database. An amendment to the study protocol describing the analysis plan and quality of the additional data source will be provided to FDA prior to conducting the Premier additional analysis. If the pooled Mercy/Mayo analysis is statistically significant and the comparative study in Premier is statistically significant then ThermoCool STSF meets the criteria for the label extension. However, given the limited power of the pooled Mercy/Mayo analysis we propose that ThermoCool STSF would also meet the criteria for a label extension if the Premier study is statistically significant and the Mercy/Mayo point estimate of the cumulative incidence of the safety endpoint is < 10% (compared to the expected complication rate of ThermoCool ST agreed to in the protocol by FDA of 7.5%). This is equivalent to 7 safety events out of 70 ischemic VT patients and an upper bound of less than 18%.

# 7 Study Duration

12 months

# 8 Alignment with NESTcc Goals

The MDUFA IV agreement requires NESTcc to pilot projects to determine the usability of RWE for expanding indications for use for products that are not currently subject to a registry. The first phase of this test case demonstrated the ability of two NESTcc Network Collaborators to capture the data elements needed, to support an adequately powered and generalizable research study. Building on this foundational work will enable the team to efficiently, with a high possibility of success, conduct a study intended to expand an indication for the products.

# 9 Appendixes

## 9.1 Appendix 1: Study ThermoCool Catheters UDIs

| Brand Name | Company Name | Version or Model | GMDN Terms | Device ID |
|---|---|---|---|---|
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134702 | Cardiac radio-frequency ablation system catheter | Primary: 10846835009781 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134802 | Cardiac radio-frequency ablation system catheter | Primary: 10846835010152 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134801 | Cardiac radio-frequency ablation system catheter | Primary: 10846835010145 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134805 | Cardiac radio-frequency ablation system catheter | Primary: 10846835010183 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134803 | Cardiac radio-frequency ablation system catheter | Primary: 10846835010169 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134703 | Cardiac radio-frequency ablation system catheter | Primary: 10846835009798 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134701 | Cardiac radio-frequency ablation system catheter | Primary: 10846835009774 |
| THERMOCOOL SMARTTOUCH SF | BIOSENSE WEBSTER INC. | D134804 | Cardiac radio-frequency ablation system catheter | Primary: 10846835010176 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D132705 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009200 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D133603 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009019 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D132701 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009163 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D133601 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835008982 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D132702 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009170 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D133602 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009002 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D132704 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009194 |
| ThermoCool SmartTouch | BIOSENSE WEBSTER INC. | D132703 | Cardiac mapping/radio-frequency ablation catheter, single-use | Primary: 10846835009187 |

## 9.2 Appendix 2: NESTcc Test Case 07 Phase 2 Work Group Core Members

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## 9.3 Appendix 3: Participating NESTcc Network Collaborators

| | Mercy Health | Mayo Clinic |
|---|---|---|
| Organization Type | Health System | Health System |
| Hospitals | 45 | 23 |
| Clinics | 350 outpatient facilities (3,000 integrated providers) | 159 |
| Patient Records | 11M (3M active patients) | 2.3M |
| Main Campuses | St. Louis, MO | Rochester, MN, Scottsdale and Phoenix, AZ, and Jacksonville, FL |
| Geographic Coverage | Missouri, Oklahoma, Arkansas, and Kansas | With referrals across country |
| Available Data Sources | EHR (Epic)<br>UDI (barcode scanning system at point of care since 2016; charge codes for device billing before 2016)<br>Pharmacies<br>Registries | EHR (Epic)<br>Supply chain database with UDI (barcode scanning)<br>Pharmacies<br>Registries (e.g., Mayo Clinic Cardiovascular AF and VT Ablation Registries) |
| PCORnet CDM | No | Yes |

## 9.4 Appendix 4: Description of Mayo Clinic AF and VT Ablation Registries

The Mayo Clinic's AF ablation registry is an internally maintained, nurse-abstracted, prospective database that is maintained by the Mayo Clinic Rochester's cardiovascular department for tracking case characteristics, volumes, operator statistics, and clinical outcomes for internal quality and research purposes. The database contains manually abstracted information regarding patient characteristics (demographics, comorbidities, geographic distribution), arrhythmia characteristics, procedure characteristics (including more than 40 items such as technique, equipment used, case duration, fluoroscopy expose, etc.), peri-procedural complications (including more than 40 items such as TIA, stroke, hemidiaphragm paralysis/involvement, pericardial effusion, tamponade/centesis, death, etc.), and long-term outcomes (complications and arrhythmia-specific outcomes). The Mayo Clinic's AF ablation registry (dating back to 1999) contains 2,178 cases in 2010-2014, 1,252 cases in 2015-2017, and 950 cases in 2018-2020.

The Mayo Clinic's VT ablation registry is an internally maintained, nurse-abstracted, prospective database that is maintained by the Mayo Clinic Rochester's cardiovascular department for tracking case characteristics, volumes, operator statistics, and clinical outcomes for internal quality and research purposes. The Mayo Clinic's VT ablation registry contains 455 cases in 2014-2015 and 930 cases in 2016-July 2019 with a total >1385 cases as of today (will continue to be updated). The data from this VT ablation registry are collected through a manual data abstraction process by clinician nurses. The database collects over 200 data elements categorized by medical history, current medications, procedure, in laboratory procedure complications (eg, dissection, tamponade/centesis, death), and follow up. For the follow up, the medication use and over 40 complications are covered, including discharge complications (1-20 days post procedure) (eg, death, tamponade/centesis) and 30 day complications (11-60 days post procedure) (eg, death, hospitalization).

## 9.5 Appendix 5: Abstract Submitted to the International Conference of Pharmacoepidemiology 2021

### COMPLETENESS OF 1-YEAR PATIENT FOLLOW-UP IN 3 HEALTHCARE SYSTEM ELECTRONIC HEALTH RECORD SYSTEMS

Background

The proportion of study patients who have data available for follow-up in electronic health records (EHRs) is an important element of validity for real-world evidence (RWE)-based studies that assess long-term clinical outcomes. Unlike claims data, EHRs do not include enrollment records. The National Evaluation System for health Technology Coordinating Center (NESTcc) was launched by the FDA in 2016 as a public-private partnership to improve the use of RWE to support regulatory decision-making for medical devices. In a NESTcc-funded study to assess the feasibility of using RWE for a label extension of cardiac ablation catheters to treat atrial fibrillation (https://nestcc.org/using-real-world-data-to-evaluate-cardiac-ablation-catheters/), we evaluated the proportion of patients who had in-person contact recorded in the EHRs of three health systems.

Objective

To assess the proportion of cardiac ablation study patients who had in-person contact after 7, 30, and 365 days post-procedure with the healthcare systems where their procedure was conducted.

Methods

Retrospective data from 3 health systems (Mayo Clinic, Mercy Health, and Yale-New Haven Hospital) from 2014 to 2019 were assessed using an algorithm of in-person contact (which included both face-to-face visits and remote contact, such as telephone visits) to determine patient follow-up rates. Patients who underwent catheter ablation for atrial fibrillation were included.

Results

A total of 10,679 patients were included: 2,901 at Mayo Clinic, 3,955 at Mercy, and 3,823 at Yale. The proportions of patients who had in-person contact that was recorded in an EHR encounter at least 7, 30, and 365 days post-ablation was the following: Mayo Clinic: 97%, 96%, 84%; Mercy: 90%, 89% and 73%; and Yale: 46%, 23% and 4%, respectively. Investigation of lower follow up at Yale identified this was likely because Yale’s electrophysiology laboratory allows non-Yale physicians to perform procedures and some Yale physicians follow patients at non-Yale clinics, and those patients’ follow-up would not be within Yale’s EHR.

Conclusions

Follow up rates in EHRs were very high at 7 and 30 days post-procedure and high at 1 year follow-up at 2 of the 3 health systems, allowing for excellent patient retention for procedural complications and long-term outcome assessments. Low follow-up data capture rates in individual health system EHRs need to be identified. Strategies to improve data capture, such as through patient-centered digital health data sharing platforms that track outcomes in multiple EHR systems, could increase the amount of available follow-up data.

## 9.6 Appendix 6: Safety Event Identification Plan through Cardiac Electrophysiologist Review: NESTcc Test Case ThermoCool Phase 2

- Analysis Working Group identifies charts to be reviewed by clinicians to identify potential safety events by applying the following criteria to the study population of interest:
    1. Diagnosis codes or procedure codes for safety events (eg, pericarditis) that may not be detected by the other 2 criteria below (#2 and #3).
        - As a specific case, for patients with heart block or complete heart block, we will only identify charts if patients did not have that diagnosis in the preceding 3 months prior to ablation
    2. Hospitalization/readmission or emergency department visit during the safety event identification period of 7 days. Please note that the day of ablation will be day 0; 7 additional days after the day of ablation will be examined. Patients will be required to be hospitalized after the discharge date of the ablation.
    3. Length of stay ≥ 48 hours during the index ablation hospitalization. Please note that the time prior to the index ablation will not be applied to this timing.

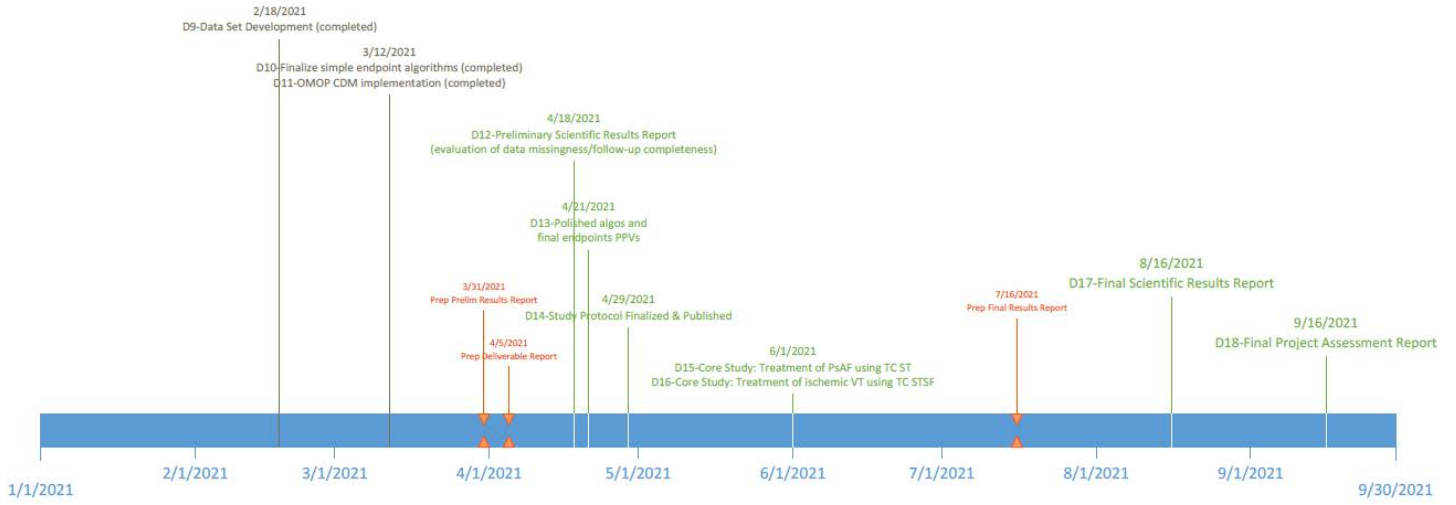
- Analysis Working Group provides Co-Investigator Cardiac Electrophysiologists (Amit Doshi, MD and Peter Noseworthy, MD) with the following, and AF ablation safety event identification and VT ablation safety event identification completed separately, since the outcomes of interest differ for these 2 procedures:
    - Patient's medical record number (sort by patient; for Mercy – group by Mercy instances of Epic)
    - Patient's name
    - Index ablation date
    - The reason(s) that the patient is being included, in 3 columns, corresponding to:
        1. Diagnosis/diagnoses (not the specific numeric ICD-9 or ICD-10 code, but rather the English language diagnosis).
        2. Hospitalization/readmission or emergency department visit during the safety event identification period of 7 days.
        3. Length-of-stay ≥ 48 hours during the index ablation hospitalization.
    - If patients are included for a hospitalization/readmission/emergency department visit or length-of-stay and have a diagnosis code present from our list of safety diagnosis codes, we will provide the diagnosis (or diagnoses) as well only if it is part of those diagnoses to be provided (e.g., pericarditis will be provided but stroke will not be).
    - If patients are included for a hospitalization/readmission/emergency department visit or length-of-stay without any diagnosis code present from our list of safety diagnosis codes, we will not provide the diagnosis for the hospitalization as well.
    - For patients that are being pulled for review based on diagnosis codes, please note if the patient has any of the various complications of interest (e.g. myocardial infarction, stroke, etc).
    - Please do not document other events that are not part of the complications of interest for these studies and use only the specific terms that are the outcomes of interest.
    - For pericardial effusion (30 days), pulmonary vein stenosis (90 days) or AEF (90 days), the diagnosis and date of diagnosis will be provided.
        - We expect to detect these rare diagnoses only by the diagnosis codes (not by review of all hospitalizations, because that would capture many unrelated hospitalizations).

- Cardiac electrophysiologist safety event identification process:
    - First, determine if the patient had the clinical event of interest diagnosed and documented by a clinician in the chart in the evaluation time period post-ablation (yes/no). This determination does not have anything to do with association with the catheter ablation, but simply if the event occurred. This should be a new event and not carried over from a history of the adverse event (i.e., prior to the index catheter ablation).
    - Second, determine if the clinical event of interest is expected to be attributed to the catheter ablation procedure (yes/no).

- Expected to always review the discharge summary, when available, and then the procedure report (since so many of the complications are peri-procedural)
- Please code all potential safety events that are identified in the patient's chart for that specific safety event identification time period.
- Please code the date of the safety event for 2 circumstances for the AF arm:
  - ≥48 hours hospital stay is the only reason for inclusion
  - If, when reviewing a chart that was pulled based on a given diagnosis, another diagnosis is identified. For example, reviewing a chart flagged for pericarditis and you also see that the patient had an MI (but the MI was not coded), then please code the date of the MI because this date will have not been available.
- Please note that for two potential safety outcomes for VT patients (1) Pericardial effusion with hemodynamic compromise and 2) Cardiac perforation), that we are using the same codes for identification of this event. Please distinguish these two distinct safety outcomes (as necessary) during the safety event identification process.

- Reviewer Concordance and Chart Distribution at Each Site
  - No physician reviewer will review a chart for which they were an operator performing the ablation
  - At each site, 10 randomly selected charts (5 each for persistent AF and VT) will be reviewed separately, with examination of concordance for uncertainty and any discussion (if necessary) to achieve concordance and standardization
  - This means only 10 charts will be reviewed by multiple physicians

## 9.7 **Appendix 7: Timeline for Study**



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