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
Industry Partner(s)	Johnson & Johnson
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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*

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

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. This study is a phase 2 study on the same medical devices and area of research as the initial feasibility study and would provide the opportunity to translate the advances and lessons learned in the feasibility study into an actual label expansion study that will be submitted to the FDA CDRH Office of Health Technology 2 (Electrophysiology).

In the feasibility study phase, the three NESTcc Data Network Collaborators (NCs) (Mercy, Mayo Clinic and Yale New Haven Health [YNHH]), and Johnson & Johnson (J&J) successfully identified the use of ThermoCool catheters using 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' electronic health record (EHR) systems and curated and evaluated the EHR system data. Based on the feasibility study results, the NCs and J&J all agree that is likely to be feasible to use the NC data at Mercy and Mayo Clinic as curated and extracted to support the evaluation of ThermoCool cardiac ablation catheters as used in new patient populations to support regulatory submissions for expanding indications of use of these catheters. We consider the work to be foundational to the use of real-world data in regulatory decision making and propose to translate the feasibility study advances to an actual label expansion study using EHR system data at Mercy and Mayo Clinic to submit it to the FDA CDRH OHT 2 (Electrophysiology) division. This could be the first medical device label expansion study using the EHR system data. The NESTcc test case has provided opportunities to interact with FDA.

Although we completed a large amount of the data evaluation effort during the feasibility study phase, a significant amount of work remains to be accomplished to develop data sets that can be used for the purpose of a label expansion, including additional work of evaluating and refining codes and algorithms for outcomes. We also need to develop comparator groups for the proposed phase 2 actual label expansion study. Because there is currently no radiofrequency ablation catheter indicated for persistent atrial fibrillation (AF), we propose the use of anti-arrhythmic drugs (AADs, which are indicated for AF) to serve as the comparator for the ThermoCool ST catheters to expand its indication for the treatment of persistent AF. For the 56-hole irrigated ThermoCool Smarttouch® SF (STSF) catheters for the treatment of ischemic ventricular tachycardia (VT), we propose the use of NaviStar® ThermoCool and ThermoCool Smarttouch® (ST) catheters as comparators since they already have ischemic VT indication.

Study Aims

The specific aims are to use retrospective real-world data from the EHR systems at Mercy and Mayo Clinic to evaluate the safety and effectiveness of ablation for 1) persistent AF and 2) ischemic VT using ThermoCool catheters.

The first indication expansion is for ThermoCool ST catheters to treat persistent AF in comparison with AAD use. An investigational device exemption (IDE) clinical study was conducted for a label expansion for ThermoCool STSF for persistent AF,[1] which is currently under review by CDRH. This real-world data study will also potentially use ThermoCool STSF as the comparator to expand the labelled indication for persistent AF for ThermoCool STSF (if approved) to ThermoCool ST, a sister catheter.

The second indication expansion is for ThermoCool STSF catheters to include an indication for the treatment of ischemic VT. An earlier version of the ThermoCool catheter, the NaviStar ThermoCool, has a label for ischemic VT, as does the ThermoCool ST catheter. This study will compare the safety and effectiveness in the treatment of ischemic VT of the ThermoCool STSF catheter in comparison to the NaviStar ThermoCool and ThermoCool ST catheters.

Study Objectives

The primary objective is to demonstrate the safety and effectiveness of ablation with ThermoCool ST catheters for the treatment of persistent AF in real-world settings in support of label expansions of these catheters.

The secondary objective is to demonstrate the safety and effectiveness of ablation with ThermoCool STSF catheters for the treatment of ischemic VT in real-world settings in support of label expansions of these catheters.

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® SF Catheters (Approved in August 2016)	• Drug refractory recurrent symptomatic paroxysmal atrial fibrillation • Type I atrial flutter in patients 18 years of age or older	Ischemic VT	NaviStar ThermoCool or ThermoCool Smarttouch Catheters (6-hole irrigated catheters)
ThermoCool Smarttouch® Catheters (Approved in February 2014)	• Drug refractory recurrent symptomatic paroxysmal atrial fibrillation • Type I atrial flutter in patients 18 years of age or older • Recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults	Persistent AF	1) Catheter Ablation Comparator Group: ThermoCool Smarttouch® SF 2) AAD Comparator Group: prescriptions for at least two different AADs
NaviStar® ThermoCool Catheters (Approved in August 2006)		None (a potential comparator)	

Study Design

This is a retrospective cohort study evaluating the safety and effectiveness of ablation for persistent AF or ischemic VT with ThermoCool catheters in usual clinical practice.

Study Population

Inclusion Criteria

- Patients aged 18 years or older will be eligible for the study if they met the following inclusion criteria:

1) For persistent AF:

Device of interest group:

- Underwent endocardial catheter ablation for persistent AF with the procedure performed using ThermoCool ST catheters

Comparator group:

- Used class I or III AAD (currently used in clinical practice) for persistent AF*
- Underwent endocardial catheter ablation for persistent AF with the procedure performed using ThermoCool STSF (a potential comparator group)

*Currently under extensive evaluation and subject to modification based on the evaluation results

2) For ischemic VT

Device of interest group:

- Underwent endocardial catheter ablation for ischemic VT with the procedure performed using ThermoCool STSF catheters

Comparator group:

- Underwent endocardial catheter ablation for ischemic VT with the procedure performed using NaviStar ThermoCool or ThermoCool ST catheters

Exclusion Criteria

- Prior cardiac surgery

Selection of Comparator Groups and Index dates for Study Groups

1) **For persistent AF**:

a. ThermoCool STSF Comparator Group:

The index date for the ThermoCool STSF comparator group would be the date of the first recorded catheter ablation for persistent AF with ThermoCool STSF catheters during the evaluation period.

b. AAD Comparator Group:

Patients in the AAD comparator group will be required to have prescriptions for at least two different AADs during the evaluation period. The index date for the AAD comparator group would be the start date of the second AAD.

c. Device of Interest (ThermoCool ST) Group:

The index date for the device of interest (ThermoCool ST) group would be the date of the first recorded catheter ablation for persistent AF with ThermoCool ST catheters during the evaluation period.

For the two ablation groups, a sensitivity analysis will be conducted among those who had at least one prescription of AAD (class I or III) prior to the index date.

All patients aged ≥18 years with a diagnosis of persistent AF prior to or at time of index events and who met the eligibility criteria described above will be considered.

In the phase 1 study, the performance of using ICD-10-CM diagnosis code of I48.1 to identify persistent AF patients from the EHR system was assessed at Mercy using a Natural Language Processing tool, which was built and validated for the AF type query previously by a manual review of notes written by cardiologists (200 positive notes [where the query found a mention of AF type] and 200 negative notes [where the query did not find a mention AF type] from each year between 2010 and 2019, for a total of 2000 positive and 2000 negative notes reviewed, with a precision of 97.8%, a recall of 98.7%, and a F-measure of 98.2%). The positive predictive value (PPV) was 80%, negative predictive value was 91%, specificity was 96%, and sensitivity was 63%. In the phase 1 study, Mayo Clinic used its internal AF ablation registry as a gold standard data evaluation source to evaluate the performance of using ICD-10-CM diagnosis code of I48.1. In the Mayo Clinic's AF ablation registry, the AF cases were classified as paroxysmal or persistent by physicians through a manual review process. For persistent AF cases identified using ICD-10-CM diagnosis code I48.1, 71% were confirmed as persistent AF cases from the registry. In the Phase 2 study, we will continue to leverage the Mayo Clinic's AF ablation

registry to evaluate and refine the codes and algorithms that will be used for identifying persistent AF patients and outcomes.

2) **For ischemic VT**:

a. NaviStar ThermoCool or ThermoCool ST Comparator Group:
The index date for the NaviStar ThermoCool or ThermoCool ST comparator group would be the date of the first recorded catheter ablation for ischemic VT using NaviStar ThermoCool or ThermoCool ST catheters, whichever occurred first, during the evaluation period.

b. Device of Interest (ThermoCool STSF) Group:
The index date for the device of interest (ThermoCool STSF) group would be the date of the first recorded catheter ablation for ischemic VT using ThermoCool STSF catheters.

All patients aged ≥18 years with a diagnosis of ischemic VT at time of index ablations with ThermoCool STSF, NaviStar ThermoCool, or ThermoCool ST catheters and who met the eligibility criteria described above will be considered. VT patients with a prior ischemic heart disease will be considered ischemic VT using the diagnosis codes of ICD-9-CM and ICD-10-CM.

All patients will be required to have certain periods of medical record data prior to the index date (referred to as the baseline or pre-index period).

Study Outcomes

Primary Safety Outcomes:
1) **For persistent AF**, similar to the IDE clinical study that was conducted for a label expansion for ThermoCool STSF for persistent AF [1]**:**

- The primary safety endpoint is the cumulative incidence (proportion) of a composite of primary adverse events (PAEs) occurring within 7 days of the initial and repeat ablation procedures using the study catheter. PAEs include death, atrioesophageal fistula, cardiac tamponade/perforation, acute MI, acute stroke/cerebrovascular accident, thromboembolism, transient ischemic attack (TIA), diaphragmatic paralysis, pneumothorax, heart block, pulmonary vein stenosis, pulmonary edema, pericarditis, and major vascular access complication or bleeding requiring transfusion. Pulmonary vein stenosis and atrioesophageal fistulas occurring greater than 7 days after the index procedure up to 3 months will also be considered and analyzed as PAEs.

2) **For ischemic VT**, similar to the Post-Approval THERMOCOOL VT (NaviStar ThermoCool Catheter for Endocardial RF Ablation in Patients With Ventricular Tachycardia) Trial[2]:

- The primary safety endpoint is the cumulative incidence (proportion) of a composite of cardiovascular-specific adverse events (CSAE) during and within 7 days post-ablation. CSAE includes cardiac perforation, pericardial effusion with hemodynamic compromise, pulmonary embolus, complete heart block, acute stroke, acute MI, new acute severe mitral or aortic regurgitation, deep venous thrombosis, arterial dissection, injury that required surgical treatment, and death.

Primary real-world effectiveness outcomes:
1) **For persistent AF:** The primary effectiveness endpoint is the incidence (rate and proportion) of a composite endpoint at 6 months and 1 year after the index date of

- Rehospitalization for AF
- Rehospitalization for heart failure

- Electrical cardioversion for AF
- Repeat ablation for AF in subjects in the ablation groups
- Ablation for AF in subjects in the AAD comparator group
- Prescription of a new AAD

2) **For ischemic VT:** The primary effectiveness endpoint is the incidence (rate and proportion) of a composite endpoint at 6 months and 1 year after the index date of

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

Consistent with treatment guidelines[3] and past approaches[4], a 3-month blanking period (healing and stabilization) for persistent AF will be implemented for the assessment of effectiveness outcomes across groups.

Table 2. Proposed safety and effectiveness outcomes for persistent AF and ischemic VT

Outcome	Persistent AF	Ischemic VT
Safety within 7 days after procedure		
	• Death • Cardiac tamponade/perforation • Acute MI • Acute stroke/cerebrovascular accident • Transient ischemic attack (TIA) • Heart block • Pericarditis • Thromboembolism • Atrioesophageal fistula* • Diaphragmatic paralysis • Pneumothorax • Pulmonary vein stenosis* • Pulmonary edema • Major vascular access complication or bleeding requiring transfusion *Pulmonary vein stenosis and atrio-esophageal fistulas occurring >7 days after the index procedure up to 3 months will also be considered and analyzed as PAEs.	• Death • Pericardial effusion with hemodynamic compromise • Cardiac perforation • Acute MI • Acute stroke • Complete heart block • Deep venous thrombosis • Pulmonary embolus • New acute severe mitral or aortic regurgitation • Arterial dissection • Injury that required surgical treatment

Effectiveness during 6 months and 1 year of follow-up after procedure	After a 3-month blanking period	
	• Rehospitalization for AF • Rehospitalization for heart failure • Repeat ablation for AF in subjects in the ablation groups • Ablation for AF in subjects in the AAD comparator group • Electrical cardioversion for AF • Prescription of a new AAD	• Rehospitalization for VT • Rehospitalization for heart failure • Repeat ablation for VT

Statistical Analysis

Prior to the outcome analysis, the 2-stage propensity score strategy will be used for selecting comparator groups within persistent AF and ischemic VT populations separately within each health system to reduce confounding in the comparison of outcomes between groups.

Firstly, the propensity score model will be developed within persistent AF and ischemic VT populations separately using the group memberships as the outcome and all important and available baseline patient demographic (e.g., age, gender, body mass index, year of the index treatment), operator experience (number of ablations 12 months prior to the index date), and clinical and comorbidity characteristics (e.g., year of first AF or VT diagnosis recorded in the database, CHA2DS2-VASc, Charlson index) as covariates in a multivariable logistic regression model for persistent AF and ischemic VT separately within each health system to generate the propensity score for each patient. The propensity score represents the likelihood that the patient was in the device of interest group (ThermoCool ST for persistent AF and ThermoCool STSF for ischemic VT).

Secondly, all subjects will be sorted by propensity scores after propensity score calculation. The quintiles of propensity scores will be defined by the distribution of propensity scores in the device of interest group (i.e., the study group not the comparator group), with approximately 20% of the device of interest group in each propensity score quintile based on the ranking of a subject's propensity score. Subjects in the comparator group will then be allocated to one of the 5 quintiles based on individual comparator patients' propensity scores. The balance of the device of interest group quintiles to the comparator group quintiles will be achieved through assigning comparator subjects to quintiles based on their propensity scores and weighting subjects using the method described by Desai et al.[5] Specifically, each exposed patient (i.e., the patient in the study group) will receive a weight of 1. Unexposed patients (i.e., patients in the comparator group) will be weighted in proportion to the distribution of the exposed in the stratum into which they will fall, and the unexposed group weights will be scaled to sum to the number of unique unexposed patients included in the analysis. This weighting creates a weighted population in which confounder distribution concordance is achieved between the exposed and unexposed groups, to the extent that it is achieved within each stratum.

$$\left(unexposed\ weights = \frac{(^{N}exposed\ in\ strata\ i/^{N}total\ exposed)}{(^{N}unexposed\ in\ strata\ i/^{N}total\ unexposed)}\right)$$

The stratified subjects will be saved in an output data set for use in a subsequent outcome analysis.

The propensity score model will be constructed after receiving the review/input/approval from FDA. An independent statistician with no access to the study outcome data will be identified to build the propensity score model and select comparator subjects using the propensity score stratification methods for persistent AF and ischemic VT separately

within each health system. Missing baseline covariates will be imputed using multiple imputation techniques before constructing the propensity score model and carrying out the outcome analyses.

To confirm the adequacy of the propensity model in improving the covariate balance between the comparison groups, the balance of the distributions of the propensity score and the adjusted covariates will be assessed numerically and graphically between the two groups prior to stratification, for all subjects across strata, and for the subjects within each stratum. The variable summary statistics between the comparison groups, including the mean difference, standardized mean difference, and variance ratio will be generated for all subjects and within each stratum. The variable summary statistics, including the mean difference of the weighted mean of the stratum means, and pooled standardized mean difference and variance ratio across strata will also be generated. The absolute standardized mean difference ≤0.1[6] and the variance ratio between 0.5 and 2[7,8] are considered to be good variable balance. In addition, standardized mean differences plots for the variables will be used to display differences based on all subjects and combining estimates across strata and within strata.

Graphical methods will be used for comparing the overlap in the distribution of the propensity score and baseline covariates between the two groups within each propensity score quintile (e.g., side by side box plots, cumulative distribution function plots, cloud plots, and non-parametric density plots for continuous variables and bar charts for binary classification variables).

The overlapping coefficient (r_s) (the area under the two probability density functions simultaneously) will be calculated for each propensity score stratum. Let f_d and f_c denote the density functions of the observed propensity score for subjects in the device of interest group and the comparator group, respectively. Then the overlapping coefficient for the s-th strata will be obtained by $r_s = \int_0^1 \min [f_d , f_c] \, de$. The standardized overlapping coefficient for each stratum will be obtained by $r_s / \sum r_s$. A diagram of propensity score distributions with the relevant areas shaded to display the overlapping will be considered.

Analysis of Baseline Demographic and Clinical Characteristics

Demographic and clinical characteristics at baseline will be summarized descriptively for subjects in each group. Standard descriptive summaries for continuous variables will include the number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum values. The count and percentage will be generated for categorical variables. Percentages will be calculated based on the number of subjects without missing data. Variables among groups will be compared descriptively before and after the propensity score stratification numerically and graphically as described above to assess the balance in the distributions.

Primary Endpoint Analysis

Primary endpoint analyses 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. Data will be standardized in the Observational Medical Outcomes Partnership (OMOP) common data model to facilitate common analyses in two data systems.

The estimate of the primary endpoints will be obtained by a weighted average across the 5 quintiles using weights for each quintile for each group in the propensity score stratified sample within persistent AF and ischemic VT populations separately within each health system. Weighted generalized linear models will be used to derive effect estimates after weighting subjects in the comparator group according to the distribution of the device of interest group in their stratum as described above[5]. Each study outcome from Mercy and Mayo Clinic will be pooled by the inverse of its variance to

generate the overall study estimate with corresponding 95% confidence interval. Chi-square or Fisher exact tests will be conducted to examine differences across pre-specified subgroups.

A detailed statistical analysis plan will be developed to get review/input/approval from FDA.

Sample Size and Power Calculation

Table 3. The number of patients who used ThermoCool catheters identified from Mercy during the feasibility study phase (phase 1) and from Mayo Clinic up to August 13, 2020

	Persistent AF		Ischemic VT			Non-Ischemic VT		
	STSF	ST	STSF	ST	NaviStar	STSF	ST	NaviStar
Mercy (01/01/2014 – 02/11/2020)	492	251	50	38	19	12	37	18
Mayo Clinic (01/01/2014 – 08/13/2020)	100	233	70	180	114	18	116	113
Total	592	484	120	218	133	30	153	131

We would expect to obtain additional 6 months of data from Mercy. Therefore, the number of patients listed above would be expected to be increased.

Recent pre-market clinical studies (IDE studies) have assumed a 7% PAE composite rate for demonstration of safety against an objective performance goal of 14%. A sample size of 105 subjects will yield 80% power for the test of the primary safety endpoint with the mid-p method[9] at the 5% significance level. Assuming an 90% follow-up rate at 7 days, a target sample size would be 117 subjects for assessing the primary safety endpoint.

Mercy is an integrated delivery network system with a network of healthcare providers and facilities within a specific geographic region that offers a full range of healthcare services and has good long-term follow-up. In the preliminary assessment in the phase 1 study, the in-person encounter percentages in patients after ablation for arrythmia with ThermoCool STSF or ThermoCool ST in the Mercy EHR system database were 91% for day 7+, 89% for day 30+, 77% for 6+ months, and 66% for 1+ year. Mayo Clinic's EHR data warehouse and the Rochester Epidemiology Project (a collaboration between health care providers in Minnesota and Wisconsin) database can be used to retrieve longer-term follow up information (e.g., 1-year follow up). We will conduct evaluations of follow-up in the Phase 2 study.

The power to assess the incidence of a composite of safety events and a composite of effectiveness events was also estimated for comparing the two proportions between two independent samples of equal size in a parallel group non-inferiority study[10].

1) **For persistent AF:**

The expected incidence of a composite of primary real-world effectiveness events is approximately 15-30% in AF[4,11,12] and VT[2,13] populations. The number of patients who used ThermoCool ST catheters in the persistent AF population in the 2 NC data systems was 484 (387 for an 80% follow-up rate and 339 for an 70% follow-up rate). For the persistent AF study, assuming a rate of 20% for a composite of effectiveness events with a one-sided type-I error of 5% and a non-inferiority margin of 10%, the power is 99% for a sample size of 484, 97% for a sample size of 387, and 95% for a sample size of 339.

2) **For ischemic VT**:

The expected incidence of a composite of primary safety events is approximately 5% in AF and VT populations (see attachment 1). The number of patients who used ThermoCool STSF catheters in the ischemic VT population in the 2 NC

data systems was 120 (108 for an 90% follow-up rate at 7 days). With a one-sided type-I error of 5% and a non-inferiority margin of 7.5%, the power is 85% for a sample size of 120 and 81% for a sample size of 108.

Study Duration
12 months

Alignment with NESTcc Goals
The MDUFA IV agreement requires NEST 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 product.

Attachment 1

Table 4. Complication Rates from the Literature

Study	Country	Data Source	Population	Number of Patients or Procedures	Complication Rate (%)
Cappato 2005 [14]	Worldwide	Survey	AF	8,745 patients	6.0
Spragg 2008 [15]	US	RWD	AF	641 procedures	5.0
Dagres 2009 [16]	Greece	RWD	AF	1,000 procedures	3.9
Cappato 2010 [17]	Worldwide	Survey	AF	16,309 patients	4.5
Bohnen 2011 [18]	US	RWD	AF	784 procedures	5.2
Bertaglia 2013 [19]	Italy	RWD	AF	2,323 patients	4.0
Deshmukh 2013 [20]	US	RWD	AF	93,801 procedures	6.3
Inoue 2014 [21]	Japan	RWD	AF	3,373 patients	4.5
Mugnai 2015 [22]	Belgium	RWD	AF	642 procedures	3.6
Yang 2017 [23]	US	RWD	AF	1,475 patients	3.9
Hosseini 2017 [24]	US	RWD	AF	39,562 procedures	7.2
Tripathi 2018 [25]	US	RWD	AF	50,969 patients	5.5
Muthalaly 2018 [26]	US	RWD RWD	AF AF	726 patients (historic cohort) 699 patients (modern cohort)	5.0 2.3
Holmqvist 2019 [27]	Sweden	RWD	AF	11,916 procedures	2.8
Wilber 2010 [28]	US, Europe, Canada, Latin America	Prospective, multicenter, randomized, unblinded, controlled trial NaviStar ThermoCool AAD	 Paroxysmal AF Paroxysmal AF	 103 patients 57 patients	 4.9 8.8
Pappone 2011 [29]	Italy	Prospective observational study ThermoCool NaviStar-RMT	Paroxysmal or persistent AF	130 patients	2.3
De Ponti 2013 [30]	Italy	Observational study Navistar ThermoCool or ThermoCool SF	AF	212 patients	2.4
Richter 2013 [31]	Austria	Non-randomized trial NaviStar ThermoCool and circular multielectrode catheter	AF	240 patients	2.9
Park 2013 [32]	Germany	Prospective, randomized, unblinded, controlled trial ThermoCool SF Navistar ThermoCool NaviStar	 AF AF	 78 patients 82 patients	 6.4 4.9
Bertaglia 2013 [33]	Italy	Multicenter, randomized, controlled study ThermoCool SF ThermoCool catheter	Paroxysmal AF Paroxysmal AF	54 patients 52 patients	0.0 3.8
Oza 2014 [34]	US	Prospective observational registry study NaviStar ThermoCool SF catheter	Paroxysmal AF	742 patients	4.0
Natale 2014 [35]	US	Prospective, multicenter, non-randomized SMART-AF trial ThermoCool ST	Paroxysmal AF	161 patients	7.5
Squara 2015 [36]	France, Belgium, Monaco	Prospective/retrospective cohort study Contact Force (CF)-sensing RF ablation cryoballoon ablation	Paroxysmal AF Paroxysmal AF	198 patients 178 patients	7.1 7.3
Reddy 2015 [37]	Europe, US	Prospective, multicenter, randomized, controlled trial	Paroxysmal AF	152 patients	7.2

		CF-sensing catheter Non-CF catheter	Paroxysmal AF	143 patients	9.1
Jourda 2015 [38]	France	Prospective, open-label, non-randomized clinical study ThermoCool ST cryoballoon ablation	Paroxysmal AF Paroxysmal AF	75 patients 75 patients	2.7 1.3
Verna 2015 [39]	12 countries	STAR AF II Trial: Prospective, randomized trial comparing 3 strategies of RF ablation	Persistent AF	568 patients	6.0
Itoh 2016 [40]	Japan	Prospective, open-label, non-randomized clinical study ThermoCool ST ThermoCool EZ Steer	Paroxysmal AF Paroxysmal AF	50 patients 50 patients	0.0 0.0
Gonna 2017 [41]	UK	ThermoCool STSF (prospective) ThermoCool SF (retrospective database)	Arrhythmia Arrhythmia	100 patients 100 patients	0.0 2.0
Chinitz 2018 [42]	US	Prospective, open-label, non-randomized SMART SF Trial ThermoCool STSF	Paroxysmal AF	159 patients	2.5
Maurer 2018 [43]	Germany	Observational study ThermoCool STSF ThermoCool ST	Paroxysmal AF Paroxysmal AF	75 patients 35 patients	2.7 0.0
Hussein 2018 [44]	UK, Italy	PRAISE study: Cohort study	Persistent AF	40 patients	0.0
Boveda 2018 [45]	Germany, France, and Greece	Prospective, multicenter, single-arm CRYO4PERSISTENT AF Trial Cryoballoon ablation	Persistent AF	101 patients	4.0
Potter 2019 [46]	Europe, Australia, Canada	Prospective, real-world, observational registry study ThermoCool ST	Persistent AF	150 patients	4.0
Mansour 2020 [1]	US, Canada	Prospective, multicenter, non-randomized PRECEPT study ThermoCool STSF	Persistent AF	348 patients	3.8
Plenge 2020 [47]	Germany	Prospective, open-label, non-randomized trial ThermoCool STST ThermoCool ST	Paroxysmal or persistent AF Paroxysmal or persistent AF	60 patients 20 patients	1.7 0.0
Su 2020 [48]	US, Canada, Japan	Prospective, multicenter, single arm STOP trial Cryoballoon ablation	Persistent AF	165 patients	0.6
Natale 2020 [49]	US	Retrospective, real-world, hospital database study ThermoCool ST or STSF cryoballoon ablation ThermoCool ST or STSF cryoballoon ablation	Paroxysmal AF Paroxysmal AF Persistent AF Persistent AF	215 patients 658 patients 192 patients 408 patients	6.0 6.1 6.3 7.8
Reddy 2007 [50]	US	Clinical trial	Ischemic VT or ventricular fibrillation	64 patients	4.7
Stevenson 2008 [51]	US	NaviStar ThermoCool catheter pre-approval VT ablation clinical study	Ischemic VT	231 patients	7.3

Marchlinski 2016 [2]	US	NaviStar ThermoCool catheter post-approval clinical study	Ischemic VT	233 patients	3.9
Bohnen 2011 [18]	US	RWD	VT with structural heart disease	249 procedures	6.0
Palaniswamy 2014 [52]	US	RWD	Ischemic VT	4,653 patients	11.2
Hosseini 2017 [24]	US	RWD	VT	9,642 procedures	9.9
Holmqvist 2019 [27]	Sweden	RWD	VT	964 procedures	4.5
Sharma 2020 [53]	US	RWD	VT	11,725 patients	8.2

Table 5. Sample Size Estimates for Achieving 80% and 90% Power

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)				Sample size per treatment group for 90% power with α=0.05 (one-sided)			
			Follow-up rate				Follow-up rate			
			No loss of follow-up	90%	80%	70%	No loss of follow-up	90%	80%	70%
A composite of primary safety events										
5%	5%	7.5%	105	117	131	150	145	161	181	207
A composite of primary real-world effectiveness events										
20%	20%	10%	198	220	248	283	274	304	343	391

Sample size was estimated for comparing the two proportions between two independent samples of equal size in a parallel group non-inferiority study (one-sided; α=0.05) for 80% and 90% power[10]. The non-inferiority margin was assumed to be 7.5% for a composite of primary safety events and 10% for a composite of primary real-world effectiveness events. Based on the feasibility study patient counts and the anticipated increase in patient numbers, statistical power is expected to be adequate.

Attachment 2

Description of Mayo Clinical AF and VT Ablation Registries

Mayo Clinical 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. In the Phase 1 study, Mayo Clinic utilized this internal registry as a gold standard data evaluation source, and the AF cases were classified as paroxysmal or persistent by physicians through a manual review process. For persistent AF cases identified using ICD-10-CM diagnosis code I48.1, 71% were confirmed as persistent AF cases from the registry. In the Phase 2 study, we will continue to leverage the Mayo Clinic's AF ablation registry to evaluate and refine the codes and algorithms that will be used for identifying persistent AF patients and outcomes.

In the Phase 2 study, we will also leverage the Mayo Clinic's VT ablation registry (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]) to evaluate the codes and algorithms used to identify ischemic VT vs non-ischemic VT patients and outcomes. The data from this VT ablation registry are collected through a manual data abstraction process by clinician nurses. The database will serve as a gold standard as the cases (e.g., ischemic VT vs. non-ischemic VT) are confirmed by clinicians through a manual review process. The database collects over 200 data elements categorized by medical history, current medications, procedure, in laboratory procedure complications (e.g., 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) (e.g., death, tamponade/centesis) and 30 day complications (11-60 days post procedure) (e.g., death, hospitalization). In addition, Mayo Clinic's EHR data warehouse and the Rochester Epidemiology Project (a collaboration between health care providers in Minnesota and Wisconsin) database can be used to retrieve longer-term follow up information (e.g., 1-year follow up).

Attachment 3

Table 6. NESTcc Test Case 07 Phase 2 Work Group Core Members

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Attachment 4

Table 7. NESTcc Network Collaborators

	Mercy Health	**Mayo Clinic**
Organization Type	Health System	Health System
Hospitals	44	23
Clinics	350 outpatient facilities (3,000 integrated providers)	200+ in 6 states
Patient Records	11M (3M active patients)	1.3M unique patients each year
Main Campuses	St. Louis, MO	Rochester, MN, Jacksonville, FL, and Scottsdale, AZ
Geographic Coverage	Missouri, Oklahoma, Arkansas, and Kansas	With referrals across country
Available Data Sources	EHR (EPIC) UDI (barcode scanning system at point of care since 2016; charge codes for device billing before 2016) Pharmacies Registries	EHR (EPIC) Supply chain database with UDI (barcode scanning) Pharmacies Registries (e.g., Mayo Clinic Cardiovascular AF and VT Ablation Registries)
PCORnet CDM	No	Yes

References

1. Mansour M, Calkins H, Osorio J, et al. PRECEPT Study: Contact Force-Sensing Catheter Safe, Effective in Treatment of Persistent AFib. JACC: Clinical Electrophysiology 2020.
2. Marchlinski FE, Haffajee CI, Beshai JF, et al. Long-Term Success of Irrigated Radiofrequency Catheter Ablation of Sustained Ventricular Tachycardia: Post-Approval THERMOCOOL VT Trial. J Am Coll Cardiol 2016;67:674-83.
3. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. J Arrhythm 2017;33:369-409.
4. Jarman JWE, Hussain W, Wong T, et al. Resource use and clinical outcomes in patients with atrial fibrillation with ablation versus antiarrhythmic drug treatment. BMC Cardiovasc Disord 2018;18:211.
5. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. Epidemiology 2017;28:249-57.
6. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083-107.
7. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci 2010;25:1-21.
8. Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. Health Services & Outcomes Research Methodology 2001;2:169-88.
9. Lancaster HO. Significance tests in discrete distributions. J Am Stat Assoc 1961;56:223-34.
10. Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. .
11. Chinitz L, Goldstein LJ, Barnow A, et al. Comparison of real-world clinical and economic outcomes between the ThermoCool((R)) SF and ThermoCool((R)) catheters in patients undergoing radiofrequency catheter ablation for atrial fibrillation. Clinicoecon Outcomes Res 2018;10:587-99.
12. Arora S, Patel H, Chinmay Jani C, et al. Impact of catheter ablation for atrial fibrillation on mortality and hospital readmission rates in patients with heart failure and reduced ejection fraction. JACC Volume 75, Issue 11 Supplement 1, March 2020. DOI: 10.1016/S0735-1097(20)30900-1.
13. Field ME, Goldstein L, Yu Lee SH, et al. Intracardiac echocardiography use and outcomes after catheter ablation of ventricular tachycardia. J Comp Eff Res 2020.
14. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;111:1100-5.
15. Spragg DD, Dalal D, Cheema A, et al. Complications of catheter ablation for atrial fibrillation: incidence and predictors. J Cardiovasc Electrophysiol 2008;19:627-31.
16. Dagres N, Hindricks G, Kottkamp H, et al. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: still cause for concern? J Cardiovasc Electrophysiol 2009;20:1014-9.
17. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:32-8.
18. Bohnen M, Stevenson WG, Tedrow UB, et al. Incidence and predictors of major complications from contemporary catheter ablation to treat cardiac arrhythmias. Heart Rhythm 2011;8:1661-6.
19. Bertaglia E, Stabile G, Pappone A, et al. Updated national multicenter registry on procedural safety of catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:1069-74.
20. Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. Circulation 2013;128:2104-12.
21. Inoue K, Murakawa Y, Nogami A, et al. Clinical and procedural predictors of early complications of ablation for atrial fibrillation: analysis of the national registry data. Heart Rhythm 2014;11:2247-53.
22. Mugnai G, Irfan G, de Asmundis C, et al. Complications in the setting of percutaneous atrial fibrillation ablation using radiofrequency and cryoballoon techniques: A single-center study in a large cohort of patients. Int J Cardiol 2015;196:42-9.
23. Yang E, Ipek EG, Balouch M, et al. Factors impacting complication rates for catheter ablation of atrial fibrillation from 2003 to 2015. Europace 2017;19:241-9.

24. Hosseini SM, Rozen G, Saleh A, et al. Catheter Ablation for Cardiac Arrhythmias: Utilization and In-Hospital Complications, 2000 to 2013. JACC Clin Electrophysiol 2017;3:1240-8.
25. Tripathi B, Arora S, Kumar V, et al. Temporal trends of in-hospital complications associated with catheter ablation of atrial fibrillation in the United States: An update from Nationwide Inpatient Sample database (2011-2014). J Cardiovasc Electrophysiol 2018;29:715-24.
26. Muthalaly RG, John RM, Schaeffer B, et al. Temporal trends in safety and complication rates of catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2018;29:854-60.
27. Holmqvist F, Kesek M, Englund A, et al. A decade of catheter ablation of cardiac arrhythmias in Sweden: ablation practices and outcomes. Eur Heart J 2019;40:820-30.
28. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010;303:333-40.
29. Pappone C, Vicedomini G, Frigoli E, et al. Irrigated-tip magnetic catheter ablation of AF: a long-term prospective study in 130 patients. Heart Rhythm 2011;8:8-15.
30. De Ponti R, Lumia D, Marazzi R, et al. Left atrial diverticula in patients undergoing atrial fibrillation ablation: morphologic analysis and clinical impact. J Cardiovasc Electrophysiol 2013;24:1232-9.
31. Richter B, Gwechenberger M, Kriegisch M, Albinni S, Marx M, Gossinger HD. Combined circular multielectrode catheter and point-by-point ablation is superior to point-by-point ablation alone in eliminating atrial fibrillation. Int J Cardiol 2013;168:3721-7.
32. Park CI, Lehrmann H, Keyl C, et al. Enhanced efficiency of a novel porous tip irrigated RF ablation catheter for pulmonary vein isolation. J Cardiovasc Electrophysiol 2013;24:1328-35.
33. Bertaglia E, Fassini G, Anselmino M, et al. Comparison of ThermoCool(R) Surround Flow catheter versus ThermoCool(R) catheter in achieving persistent electrical isolation of pulmonary veins: a pilot study. J Cardiovasc Electrophysiol 2013;24:269-73.
34. Oza SR, Hunter TD, Biviano AB, et al. Acute safety of an open-irrigated ablation catheter with 56-hole porous tip for radiofrequency ablation of paroxysmal atrial fibrillation: analysis from 2 observational registry studies. J Cardiovasc Electrophysiol 2014;25:852-8.
35. Natale A, Reddy VY, Monir G, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. J Am Coll Cardiol 2014;64:647-56.
36. Squara F, Zhao A, Marijon E, et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. Europace 2015;17:718-24.
37. Reddy VY, Dukkipati SR, Neuzil P, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. Circulation 2015;132:907-15.
38. Jourda F, Providencia R, Marijon E, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. Europace 2015;17:225-31.
39. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812-22.
40. Itoh T, Kimura M, Tomita H, et al. Reduced residual conduction gaps and favourable outcome in contact force-guided circumferential pulmonary vein isolation. Europace 2016;18:531-7.
41. Gonna H, Domenichini G, Zuberi Z, et al. Initial clinical results with the ThermoCool(R) SmartTouch(R) Surround Flow catheter. Europace 2017;19:1317-21.
42. Chinitz LA, Melby DP, Marchlinski FE, et al. Safety and efficiency of porous-tip contact-force catheter for drug-refractory symptomatic paroxysmal atrial fibrillation ablation: results from the SMART SF trial. Europace 2018;20:f392-f400.
43. Maurer T, Rottner L, Makimoto H, et al. The best of two worlds? Pulmonary vein isolation using a novel radiofrequency ablation catheter incorporating contact force sensing technology and 56-hole porous tip irrigation. Clin Res Cardiol 2018;107:1003-12.

44. Hussein A, Das M, Riva S, et al. Use of Ablation Index-Guided Ablation Results in High Rates of Durable Pulmonary Vein Isolation and Freedom From Arrhythmia in Persistent Atrial Fibrillation Patients: The PRAISE Study Results. Circ Arrhythm Electrophysiol 2018;11:e006576.
45. Boveda S, Metzner A, Nguyen DQ, et al. Single-Procedure Outcomes and Quality-of-Life Improvement 12 Months Post-Cryoballoon Ablation in Persistent Atrial Fibrillation: Results From the Multicenter CRYO4PERSISTENT AF Trial. JACC Clin Electrophysiol 2018;4:1440-7.
46. Potter T, Herendael HV, Balasubramaniam R, et al. Safety and Long-Term Success of Persistent Atrial Fibrillation Ablation Using THERMOCOOL SMARTTOUCH(R) Catheter: Real-World Experience. J Atr Fibrillation 2019;12:2126.
47. Plenge T, van den Bruck JH, Luker J, Sultan A, Steven D. Porous tip contact force-sensing catheters for pulmonary vein isolation: performance in a clinical routine setting. J Interv Card Electrophysiol 2020;57:251-9.
48. Su WW, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial. Heart Rhythm 2020.
49. Natale A, Mohanty S, Goldstein L, Gomez T, Hunter TD. Real-world safety of catheter ablation for atrial fibrillation with contact force or cryoballoon ablation. J Interv Card Electrophysiol 2020.
50. Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med 2007;357:2657-65.
51. Stevenson WG, Wilber DJ, Natale A, et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation 2008;118:2773-82.
52. Palaniswamy C, Kolte D, Harikrishnan P, et al. Catheter ablation of postinfarction ventricular tachycardia: ten-year trends in utilization, in-hospital complications, and in-hospital mortality in the United States. Heart Rhythm 2014;11:2056-63.
53. Sharma P, Tripathi B, Naraparaju V, et al. Short term outcomes associated with inpatient ventricular tachycardia catheter ablation. Pacing Clin Electrophysiol 2020.