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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): [NCT01385202 - THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Reproduction analysis of the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial

Narrative Summary:

Our primary research focus will be re-analysis and reproduction of the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment . We aim to reproduce the results by explicitly following the stated methods and to apply these to trial data collected through the YODA database. The results of this exercise will be used to identify challenges and opportunities to reproducibility research in cardiovascular medicine, which is likely to become more important as more data become available. Our ultimate objective is to ensure greater confidence in trial results that lead to advances in research and improvements in human health.

Scientific Abstract:

Background: Reproduction of research findings has been identified as one potential area to reduce waste and improve efficiency in research. (1) Our team at the Cochrane Heart Group US Satellite at Northwestern University is interested in developing skills for reproducibility research to understand the challenges and opportunities to improve the process of research reproduction in cardiovascular medicine. The Yale Open Data Access (YODA) project includes one trial within cardiovascular medicine that is eligible for reproduction.

Objective: To conduct an independent reproduction and re-analysis of results from the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial (NCT01385202). Reproduction and re-analysis will be completed utilizing data collected through the YODA Project platform.

Study Design: Re-analysis of a randomized, controlled clinical trial.

Participants: Patients selected into and studied in the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial.

Main Outcome Measures: Arrhythmia free survival.

Statistical Analysis: We will evaluate the frequencies of baseline demographics and clinical/procedural characteristics of trial participants as mean (SD) or n (%). We will compare reported study results with our results using Fisher's exact test, Chi-squared test, two-sample t-test, or Wilcoxon sign rank test, as appropriate. We will plot Kaplan-Meier survival curves along with the corresponding 95% confidence intervals based on the available data.

Brief Project Background and Statement of Project Significance:

In January of 2015, the National Academy of Medicine (NAM) released a report titled Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. (2) One of the guiding principles described in this report was to increase public trust in clinical trials and promote sharing of trial data. There has recently been increasing recognition that the results of many studies (basic science, pre-clinical, and clinical research alike) published in high-profile journals cannot be reproduced or replicated, a dilemma labeled by some as the reproducibility crisis. (3) Similarly, reports have shown that there is little re-analysis conducted of the medical literature, and when re-analysis does occur, it is often completed by members of the original authorship and is therefore not independent.(4) Furthermore, re-analyses often have different findings than the original report; for instance a large systematic review of reanalysis trials found that 35% of published reanalysis papers came to different conclusions than the original paper.(4) This is a notable finding because reproducibility of results and independent verification are considered important pillars of the scientific method. In response, there has been a large push among many in the scientific community, including the NAM, to create more open and public access to large clinical trial data.

One of the main challenges in the open data initiative has been the lack of platforms to house and distribute data in an efficient and accessible manner. The Yale University Open Data Access (YODA) Project, along with their Data Holder partners, is focused on research transparency, which is an important step towards achieving the principles listed in the NAM report.(5) Our primary research focus will be re-analysis and reproduction of trial results requested through the YODA database. We aim to reproduce the results by explicitly following the methods laid out within the text of the article, as well as any online supplements, and to apply these methods to the data collected

through the YODA database. The results of this exercise will be used to identify challenges and opportunities to reproducibility research in cardiovascular medicine, which is likely to become more important as more data become available. Our ultimate objective is to ensure greater confidence in trial results that lead to advances in research and improvements in human health.

Specific Aims of the Project:

SPECIFIC AIM 1: To reproduce the results of the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial.

Our primary hypothesis is that we will be able to reproduce the results of the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial.

EXPLORATORY AIM 2: To identify the challenges and opportunities of reanalysis through the reproduction of results from the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial.

Because this aim is exploratory, we do not have a pre-specified hypothesis. Our primary objective from this aim will be to develop solutions that overcome potential challenges and accentuate opportunities for more effective reproducibility research in cardiovascular medicine.

What is the purpose of the analysis being proposed? Please select all that apply. Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety

Research Methods**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

We will include data from the THERMOCOOL® SMARTTOUCH™ Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation trial (n=172 total participants; 161 participants in the safety cohort; 122 participants in the effectiveness cohort), which has been archived in YODA for this study.

Main Outcome Measure and how it will be categorized/defined for your study:

Primary Outcome Measures:

1. The primary effectiveness endpoint for this study will be freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes through 12-month follow-up (includes a three month blanking period).
2. Primary adverse events (AE) include death, myocardial infarction (MI), pulmonary vein (PV) stenosis, diaphragmatic paralysis, atrio-esophageal fistula, transient ischemic attack (TIA), stroke / cerebrovascular accident (CVA), thromboembolism, pericarditis, cardiac tamponade, pericardial effusion, pneumothorax, atrial perforation, vascular access complications, pulmonary edema, hospitalization (initial and prolonged), and heart block.

Secondary Outcome Measures:

Rate of acute success, defined as confirmation of entrance block in all pulmonary veins (PV).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

This study describes the safety and effectiveness of an irrigated-tip ablation catheter without a comparator group. Therefore, our interest will be comparison between the primary and secondary outcomes reported by the study authors and by our team.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

The following covariates were included in the primary study report, and we will report frequencies for each.

- Gender (male vs. female)
- Age (date of birth)
- Number of atrial fibrillation paroxysms in month preceding treatment
- Number of operators during treatment
- Previous treatment with antiarrhythmic drugs
- Prevalence of hypertension (SBP \geq 140)
- Prevalence of diabetes (FPG \geq 126 or on Diabetic medications)
- Prevalence of coronary artery disease (medical history or self-report)

- Left atrial diameter (echocardiography)
- Left ventricular ejection fraction (echocardiography)
- Length of procedure time (minutes)
- Number and type of ablation (left superior pulmonary vein, right superior pulmonary vein, left inferior pulmonary vein, right inferior pulmonary vein, left common pulmonary vein)
- Prevalence of atrial flutter
- Adverse events (air or thrombotic embolism, acute PV stenosis, tamponade, phrenic nerve palsy, gastroparesis, catheter entrapment, major bleeding, or local hematoma requiring surgery)
- Induced atrial fibrillation
- Recurrence of atrial fibrillation (occurrence and length of time in days)

Statistical Analysis Plan:

We will evaluate the frequencies of baseline demographics and clinical/procedural characteristics of trial participants as mean (SD) or n (%). We will compare reported study results with our results using Fisher's exact test, Chi-squared test, two-sample t-test, or Wilcoxon sign rank test, as appropriate. We will plot Kaplan-Meier survival curves along with the corresponding 95% confidence intervals based on the available data.

Project Timeline:

Start Date: June 2016

Analysis Completion: August 2016

Manuscript Draft: October 2016

Submission: December 2016

Report to YODA: March 2017

Dissemination Plan:

We propose submission of a brief report to a specialty journal with interest in research methodology, such as *Circulation Cardiovascular Quality and Outcomes*, *Circulation Research*, *JAMA Cardiology*, or other similar journals.

Bibliography:

1. Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet*. 2014 Jan 11;383(9912):166–75.
2. Committee on Strategies for Responsible Sharing of Clinical Trial Data, Board on Health Sciences Policy, Institute of Medicine. *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*. Washington (DC): National Academies Press (US); 2015.
3. Begley CG, Ioannidis JP. Reproducibility in science: improving the standard for basic and preclinical research. *Circ Res*. 2015 Jan 2;116(1):116-26.
4. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, Ioannidis JP. Reanalyses of randomized clinical trial data. *JAMA*. 2014 Sep 10;312(10):1024-32.
5. Doshi P, Vedula SS, Li T. YODA and truth seeking in medicine. *BMJ*. 2013;347:f4251.