Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	ArcticLine Feasibility Study
Sponsor/Local Sponsor	**United States** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518 **Canada** Medtronic of Canada 99 Hereford Street Brampton, Ontario, L6Y 0R3 +1-905-460-3800
Document Version	3.0

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Christopher Anderson, Principal Statistician, CRHF
2.0	Updated the projected sample size to 20 subjects wherever applicable. Updated calculations for analysis to test assumptions underpinning primary analysis (section 7.2.2) Provided details on handling aborted freezes when calculating application-level metrics for ancillary objective 6 (section 7.2.8) Added clarification on interim analysis requirements (7.6)	Christopher Anderson, Principal Statistician, CRHF
3.0	Updating to align with CIP version 5.0	Jeff Murphy, Senior Statistician, CRHF

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAD	Antiarrhythmic Drug; specifically of class I and III
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
CEC	Clinical Events Committee
CRF	Case Report Form
CTI	Cavotricuspid Ithsmus
DCCV	Direct Current Cardioversion
IRB	Institutional Review Board
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

3. Introduction

The purpose of the ArcticLine Feasibility study is to collect preliminary safety and effectiveness data on the ArcticLine Catheter when used to treat persistent Atrial Fibrillation (AF) and right atrial Cavotricuspid Isthmus (CTI) dependent atrial flutter ("typical atrial flutter"). These data will be used to guide subsequent product development activities for the ArcticLine Catheter, including feedback on device design and input into a future pivotal study.

The principal end of the Statistical Analysis Plan (SAP) for the ArcticLine Feasibility study is to provide pre-analysis documentation and rationale for the statistical procedures that will be used in the planned analyses performed throughout this investigation. Specifically, this plan outlines methods used in this study's pre-planned interim safety report(s) and final report. It does not limit the analysis that will be completed, as further analysis beyond what is specified in this document may occur.

This SAP was developed based on version 5 of the ArcticLine Feasibility Study Clinical Investigation Plan (referred to as the CIP in this SAP), finalized on 08-JUL-2019. Excerpts from the annotated Case Report Form (CRF) document, which was last updated on 09-AUG-2018, are included in several places within this SAP.

4. Study Objectives

4.1 Primary Objective

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure-related Serious Adverse Events (SAEs) with an onset date within 7 days post-procedure.

Primary Endpoint

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, with an onset date within 7 days post-procedure (except as noted below), as adjudicated by the Clinical Events Committee (CEC), described as follows:

- Atrioesophageal fistula*

  * Includes atrioesophageal fistula with an onset date at any time after the study cryoablation procedure and is adjudicated by the CEC as either ArcticLine Catheter-related or ArcticLine cryoablation procedure-related.

- Cardiac perforation/tamponade
- Cerebrovascular accident
- Death
- Esophageal injury
- Major bleeding

- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing at hospital discharge)
- Transient ischemic attack
- Vagal nerve injury resulting in esophageal dysmotility or gastroparesis
- Vascular access complications

4.2 Ancillary Objectives

4.2.1 Ancillary Objective #1

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the left atrial roof and posterior wall in patients with demonstrated entrance block of all pulmonary veins and who underwent roof and posterior wall ablation with ArcticLine.

Ancillary Endpoint #1

Subjects must have confirmed block at the roof line and posterior wall line via periprocedural assessment of posterior wall isolation at the completion of the cryoablation procedure to be considered an acute treatment success.

4.2.2 Ancillary Objective #2

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the mitral isthmus in patients who underwent mitral isthmus ablation with ArcticLine.

Ancillary Endpoint #2

Subjects must have confirmed bi-directional conduction block at the mitral isthmus line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

4.2.3 Ancillary Objective #3

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the CTI in patients who underwent CTI ablation with ArcticLine.

Ancillary Endpoint #3

Subjects must have confirmed bi-directional conduction block at the CTI line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

4.2.4 Ancillary Objective #4

Characterize chronic treatment success of the ArcticLine Catheter in patients with demonstrated entrance block of all pulmonary veins.

Ancillary Endpoint #4

Chronic treatment success is the opposite of chronic treatment failure. Treatment failure is any of the following:

- AF/AFL/AT episodes of at least 30 seconds duration from the end of the 90 day blanking period through the 6 month visit.
- Per section 8.6.1 for the CIP, the initiation of a new Class I or III Antiarrhythmic Drug (AAD) after the 90 day blanking period, or a dose increase in an already prescribed Class I or III AAD after the 90-day blanking period. (Further details on treatment failures due to repeat ablations are specified in section 7.2.6.)
- Reablation for the treatment of recurrent AF/AT/AFL after the 90 day blanking period. (Further details on treatment failures due to repeat ablations are specified in section 7.2.6.)

4.2.5 Ancillary Objective #5

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure related serious adverse events (SAE) through the 6 month visit.

Ancillary Endpoint #5

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, as adjudicated by the Clinical Events Committee (CEC).

4.2.6 Ancillary Objective #6

Characterize procedural data:

- Total procedure time
- Total ArcticLine Catheter use time
- Left atrial dwell time
- Total fluoroscopy time
- Total fluoroscopy time during ArcticLine Catheter use
- Application duration

- Number of applications
- Fluoroscopy dose

Ancillary Endpoint #6

- Total procedure time is defined as time from first venous access to time of last catheter removal.
- Total ArcticLine Catheter use time is defined as cumulative time from each introduction of ArcticLine Catheter into the body to its removal.
- Left atrial dwell time is defined as time from transseptal puncture to time of removal of last sheath/catheter from the left atrium.
- Total fluoroscopy time is defined as total fluoroscopy time used during the procedure.
- Total fluoroscopy time during ArcticLine Catheter use is defined as the cumulative fluoroscopy time from each introduction of ArcticLine Catheter into the body to its removal.
- Application duration is defined as total duration in which cryoablation from the ArcticLine Catheter is applied to cardiac tissue overall and individually to each target area.
- Number of applications is defined as the total number of times in which the ArcticLine Catheter was used to ablate cardiac tissue overall and individually to each target area.
- Total fluoroscopy dose is defined as the amount of radiation deposited into the tissue, measured in Gy or mGy units.

4.2.7 Ancillary Objective #7

Estimate the incidence of adverse events (AEs) through the 6 month visit.

Ancillary Endpoint #7

Characterize adverse events through the 6 month visit, described as follows:

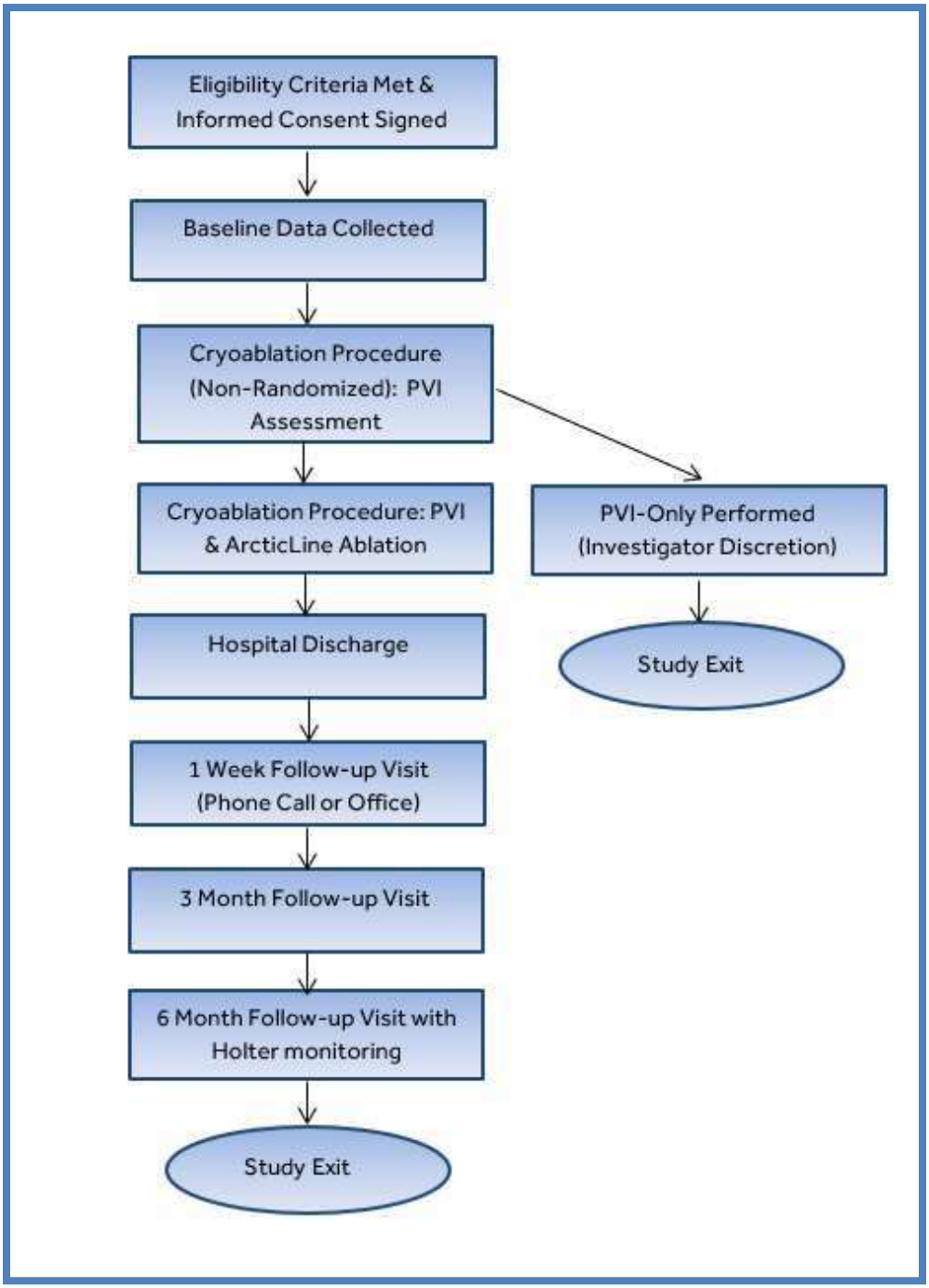
- Atrioesophageal fistula
- Cardiac perforation/tamponade
- Cerebrovascular accident
- Coronary artery spasm
- Death
- Esophageal injury
- Lung injury (including hemoptysis)
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing from hospital discharge)
- Pulmonary vein stenosis

- Symptomatic persistent iatrogenic atrial septal defect
- Transient ischemic attack
- Vagal nerve injury
- Vascular access complications

5. Investigation Plan

The purpose of the study is to collect preliminary safety and effectiveness data on the ArcticLine Catheter when used to treat persistent AF and right atrial CTI dependent AFL, or “typical atrial flutter”. These data will be used to guide subsequent product development activities for the ArcticLine Catheter, including feedback on device design and input into a future pivotal study.

Medtronic is sponsoring the ArcticLine Feasibility Study: a prospective, interventional, multicenter, non-randomized, single arm, unblinded clinical study. The study design diagram is shown in Figure 1. Up to 15 subjects will be enrolled in up to 4 centers in the United States and Canada, and will be treated with the ArcticLine Catheter.



6. Determination of Sample Size

The expected sample size is approximately 15 subjects, and is based on historical precedent for other feasibility studies, rather than a statistical derivation. The sample size of 15 treated subjects for this study was chosen with the goal to collect preliminary safety and effectiveness data on the ArcticLine

Catheter's use in both the left and right atrium. Assuming there are 15 ArcticLine cryoablation procedures in the study and the ArcticLine cryoablation procedure-related SAE rate is 6.7% (1/15 subjects: the rate of cryoablation procedure events in the STOP AF pivotal trial [PMA #P100010] was 3.1%), the exact 95% confidence interval will have a width of 32%.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subjects included in the primary analysis cohort require all of the following conditions: eligibility, consent to be studied, assessment for treatment of one or more pulmonary veins, and ablation with the ArcticLine Catheter. The study will collect data on subjects who consented to be studied and to the procedure, but who were given a different treatment at the time of operation (e.g. PVI only), but these cases will not affect the analysis of primary or ancillary objectives, as they do not meet the criteria of undergoing an ArcticLine ablation.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be described using frequency tables and listings. At stated above in section 7.1.1, subjects will be excluded from analysis of primary or ancillary endpoints if any of these conditions apply:

* Subject does not meet the study's entry criteria at the time of the procedure
* Subject did not consent to the procedure
* Subject did not undergo a procedure with the ArcticLine Catheter.

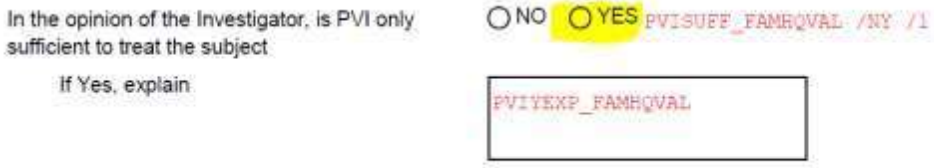
Handling of visit window and rhythm monitoring deviations as it affects the study's ancillary endpoint #4 is discussed further in section 7.2.6.

7.1.3 Analysis Sets

The **'Full Analysis Set'** consists of all enrolled and consented subjects. The Full Analysis Set will not be used for any pre-planned objectives; its principal use is in reporting adverse events that occur prior to the procedure. It can also be used in describing enrolled subjects who did not proceed to the index cryoablation procedure, if necessary, although no such analysis is currently planned.

The **'All Treated'** dataset is the subset of consented subjects meeting all inclusion and exclusion criteria at the time of the index ablation procedure who undergo a cryoablation procedure. It consists of subjects not treated with ArcticLine after the initial cryoablation assessment (the **'PVI Only'** subset) as well as subjects treated with the ArcticLine catheter. Subjects in the PVI only subset will be identified by

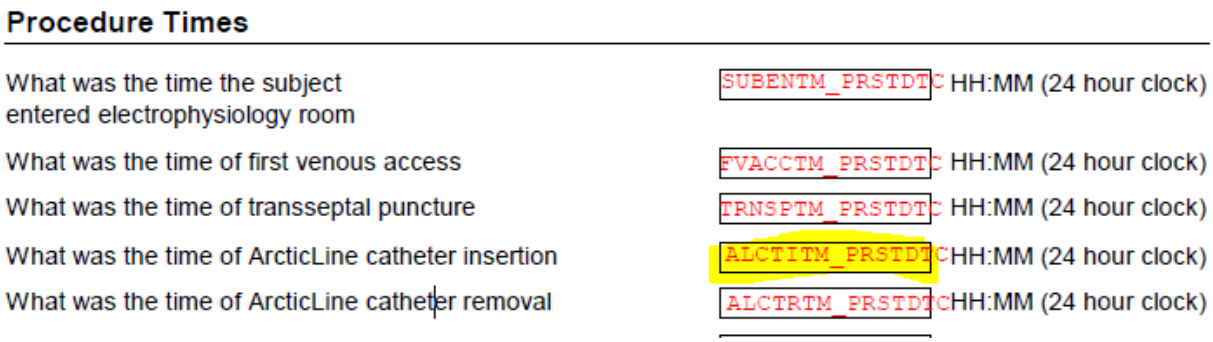
a response of 'Yes' to the question 'In the opinion of the investigator, is PVI only sufficient to treat the subject?' on the Administrative Information section of the PROCEDURE Case Report Form (CRF):



There are no pre-planned uses for the All Treated and PVI Only datasets, other than in description of subject disposition in interim, annual and final reports, and publications.

The **'ArcticLine Treated'** dataset consists of the subjects from the 'All Treated' dataset who have an ArcticLine catheter inserted into the vasculature. The ArcticLine Treated dataset will be the main analysis cohort for this study, used in the analysis of all primary and ancillary objectives.

Determination of whether an ArcticLine catheter was inserted into the vasculature will be made based on observing a completed value for "What was the time of ArcticLine catheter insertion" in the Procedure Times section of the PROCEDURE CRF:



Subjects cannot be in both the PVI Only and ArcticLine Treated datasets. Any disagreements or ambiguities in which of the two subsets of treated subjects any ablation case resides must be resolved prior to analysis.

7.2 General Methodology

7.2.1 Overview

The population of interest in this study is patients with drug refractory and symptomatic persistent AF who are treated by ablation with an ArcticLine Catheter. The sample of subjects from this population enrolled in this study will be followed for up to 6 months.

The analysis described in this SAP will be conducted by Medtronic statisticians. The study's primary endpoint (ArcticLine procedure-related Serious Adverse Events, defined below) and onset dates will be adjudicated by the Clinical Events Committee (CEC). CEC determinations will also be used to determine AE severity and procedure or device-relatedness. Adjudication of arrhythmia monitoring events, used in the calculation of ancillary objective #4 (chronic treatment success) will be performed by a core lab. While recurrence events and event times will be determined by the core lab, other components of the chronic treatment success ancillary endpoint, such as medication failures, will be determined by Medtronic study team personnel.

There is no formal hypothesis test associated with the primary objective, or for any ancillary objectives, of this study. While this SAP does not preclude all hypothesis testing, any hypotheses that are tested will be considered unplanned and/or exploratory in nature.

As this is a feasibility study, analysis of accruing data will be allowed. Interim analyses are planned at the following time points (though only select objectives may be analyzed at the first 2 analyses):

- After completion of the 15 subject index procedures and 1 week follow-up visit
- After completion of all subject follow-up visits through at least the 6 month follow-up visit, and after all subjects have been exited from the study

Further details on interim analysis are found in section 7.6. Additional exploratory analyses of the data may be conducted as deemed appropriate.

7.2.2 Primary Objective

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure related Serious Adverse Events (SAEs) with an onset date within 7 days post-procedure.

Endpoint Definition

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, with an onset date within 7 days post-procedure (except as noted below), as adjudicated by the Clinical Events Committee (CEC), described as follows:

- Atrioesophageal fistula*

  * Includes atrioesophageal fistula with an onset date at any time after the study cryoablation procedure and is adjudicated by the CEC as either ArcticLine Catheter related or ArcticLine cryoablation procedure-related.

- Cardiac perforation/tamponade
- Cerebrovascular accident
- Death
- Esophageal injury
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing at hospital discharge)
- Transient ischemic attack
- Vagal nerve injury resulting in esophageal dysmotility or gastroparesis
- Vascular access complications

The percentage of catheter related and cryoablation procedure related SAEs will be calculated as the number of procedures with at least one SAE meeting the endpoint definition divided by the number of cryoablation procedures. Exact methods will be used to construct a 95% confidence interval for the percentage of procedures with an SAE.

Each procedure will count towards the primary endpoint, so subjects with repeat ArcticLine ablations will contribute more than once to the denominator.

Sensitivity Analysis: Independence of Primary Events

Note: With version 3 of this SAP, all procedures are complete. No repeat ablations have been or will be performed, so this sensitivity analysis will not be performed.

The use of exact (Clopper-Pearson) methods of describing the binomial rate of ArcticLine procedure-related SAE's, and the associated 95% confidence interval, requires the condition of independent events. This condition is not met if primary endpoint events are more likely (or less likely) to occur in subjects who have already experienced them at their index ablation, or if all second ablations are more (or less) prone to endpoint events relative to index ablations. It is assumed that (A) the expected rates of primary safety events will be what was observed in previous Medtronic cryoablation studies (<5%), (B) the expected rate of repeat ablations is<15%, and (C) N = 15 subjects. Under these conditions, the first test of the independence assumption will be to check for any observation of *even a single subject* with primary safety events resulting from both an index ablation and subsequent repeat ablation. Observing one or more such subjects is sufficiently unlikely under conditions of independence of events within subjects (see statistical appendix for details). The second test performed will be to show independence of primary event rates between index and repeat ablations with Fisher's exact test. Under conditions of independence, a Fisher's exact test of event rates between first and second ArcticLine ablations should show p >0.05. If either the event rate is associated with repeat ablations, or the event rate is not independent within subject, primary safety events will not be pooled between index and repeat

ablations, and instead will be reported separately. This analysis will be omitted if there are no primary endpoint events resulting from repeat ArcticLine ablation procedures.

Determination of Subjects for Analysis

All ArcticLine cryoablation procedures will be included. An ArcticLine cryoablation procedure is considered to have occurred once the ArcticLine Catheter is introduced into the vasculature.

7.2.3 Ancillary Objective 1

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the left atrial roof and posterior wall in patients with demonstrated entrance block of all pulmonary veins and who underwent roof and posterior wall ablation with ArcticLine.

Ancillary Endpoint #1

Subjects must have confirmed block at the roof line and posterior wall line via periprocedural assessment of posterior wall isolation at the completion of the cryoablation procedure to be considered an acute treatment success.

Analysis Methods

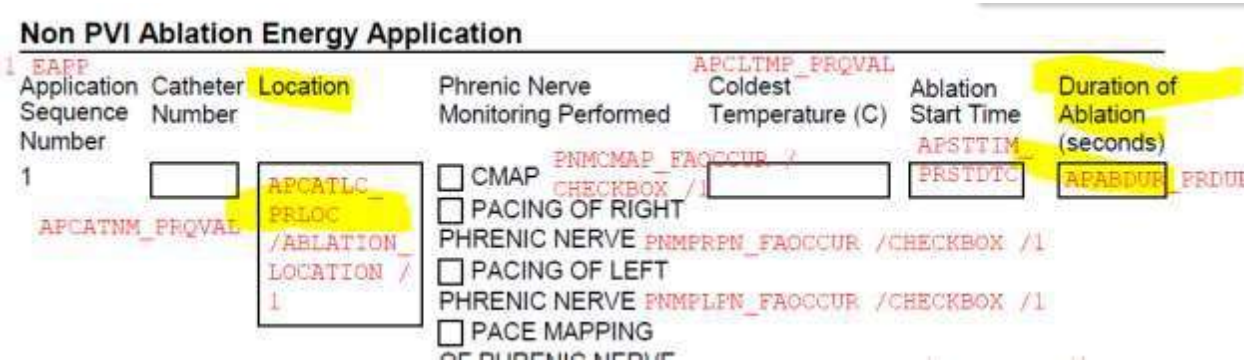
The percentage of acute roof/wall treatment successes will be calculated as:

(the number of subjects with roof/wall index procedures achieving success)

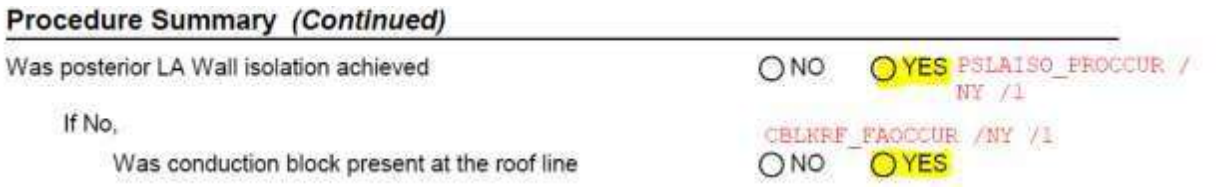
divided by

(the number of subjects with index ArcticLine cryoablation procedures where a roof or wall ablation was attempted).

An attempted roof or wall ablation is considered to have occurred once an ArcticLine cryoapplication begins, as evidenced on the NON PVI ABLATION ENERGY APPLICATION CRF by a positive duration of application where the location is either “POSTERIOR WALL, LEFT ATRIUM” or “ROOF, LEFT ATRIUM”:



To be included in the numerator, a subject must have posterior LA wall isolation at the roof line marked as ‘YES’ on the Procedure CRF:



The point estimate of the acute treatment success rate of roof/wall ablations will be reported along with its corresponding exact (Clopper-Pearson) 95% confidence interval.

Determination of Subjects for Analysis

All subjects with index ArcticLine cryoablation procedures where a roof or wall ablation was attempted will be included in this metric.

7.2.4 Ancillary Objective 2

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the mitral isthmus in patients who underwent mitral isthmus ablation with ArcticLine.

Ancillary Endpoint #2

Subjects must have confirmed bi-directional conduction block at the mitral isthmus line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

Analysis Methods

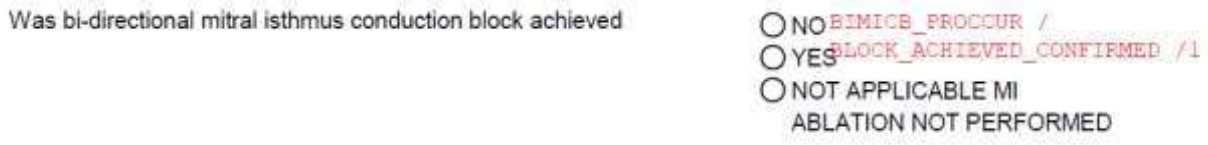
The percentage of acute mitral isthmus line treatment successes will be calculated as:

(the number of subjects with mitral line index procedures achieving success)

divided by

(the number of subjects with index ArcticLine cryoablation procedures where a mitral isthmus line was attempted).

This includes any subject for whom the NON PVI ABLATION ENERGY APPLICATION CRF indicates a positive duration of application where the location is “MITRAL VALVE ISTHMUS OR LINE”, or who has a value of “NO” or “YES” indicated in response to the Prcoedure CRF question “Was bi-directional mitral isthmus conduction block achieved?”:



To be included in the numerator, a subject must have “YES” indicated in response to the same question.

The point estimate of the acute treatment success rate of mitral isthmus ablations will be reported along with its corresponding exact (Clopper-Pearson) 95% confidence interval.

Determination of Subjects for Analysis

All subjects with index ArcticLine cryoablation procedures where a mitral isthmus line was attempted will be included in this metric.

7.2.5 Ancillary Objective 3

Estimate the percentage of patients with acute treatment success of the ArcticLine Catheter at the CTI in patients who underwent CTI ablation with ArcticLine.

Ancillary Endpoint #3

Subjects must have confirmed bi-directional conduction block at the CTI line via periprocedural assessment at the completion of the cryoablation procedure to be considered an acute treatment success.

Analysis Methods

The percentage of acute CTI line treatment successes will be calculated as:

(the number of subjects with CTI line index procedures achieving success)

divided by

(the number of subjects with index ArcticLine cryoablation procedures where the CTI line was attempted).

The denominator includes any subject for whom the NON PVI ABLATION ENERGY APPLICATION CRF indicates a positive duration of application where the location is “CAVOTRICUSPID ISTHMUS” or any subject with a “NO” or “YES” response to the Procedure CRF question “Was bi-directional block confirmed at the cavo-tricuspid isthmus (CTI)?”:

To be included in the numerator, a subject must have “YES” indicated in response to the same question. The point estimate of the acute CTI line ablation treatment success rate will be reported along with its corresponding exact (Clopper-Pearson) 95% confidence interval.

Determination of Subjects for Analysis

All subjects with index ArcticLine cryoablation procedures where the CTI line was attempted will be included in this metric.

7.2.6 Ancillary Objective 4

Characterize chronic treatment success of the ArcticLine Catheter in patients with demonstrated entrance block of all pulmonary veins.

Ancillary Endpoint #4

Chronic treatment success is the opposite of chronic treatment failure. Treatment failure is any of the following:

- AF/AFL/AT episodes of at least 30 seconds duration from the end of the 90 day blanking period through the 6 month visit.
- Per section 8.6.1 of the CIP, the initiation of a new Class I or III Antiarrhythmic Drug (AAD) after the 90 day blanking period, or a dose increase in a previously failed Class I or III AAD after the 90-day blanking period
- Reablation for the treatment of recurrent AF/AT/AFL after the 90 day blanking period

Note: For subjects who did not receive CTI ablation with ArcticLine Catheter, documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter during follow-up will not contribute to this endpoint. Subjects who (A) have "NOT APPLICABLE, CTI ABLATION NOT PERFORMED" indicated on all Procedure CRF's, and (B) only have arrhythmia occurrences that the core lab determines to be typical CTI-dependent atrial flutter (as indicated in the recurrence type field on the core lab CRF; see below) will not be considered as chronic treatment failures on grounds of AFL recurrence. They may still experience chronic treatment failure for AF or AT, atypical atrial flutter, medication failures or repeat ablations outside of the blanking period.

Does the Assessment Indicate Recurrence of AF/ AFL/ AT	If Yes, Recurrence Type
LOV (2)	☐ ATRIAL FIBRILLATION ☐ ATRIAL FLUTTER, CTI-DEPENDENT ☐ ATRIAL FLUTTER, OTHER TYPE ☐ ATRIAL TACHYCARDIA

Medication failures will be determined by calculating the pre-ablation maximum ongoing dose for each generic drug name (using TMS classification) for each patient. All medications described as "ongoing"

will be assumed to continue for all future days a subject is under study, unless an update to the medication log indicates otherwise. Drug names not observed in a patient's failed medication history on the Baseline CRF, and not observed in the medication log will be assumed to have a pre-ablation maximum ongoing dose of 0 mg/day. Treatment failures will occur on the first day a subject's daily dose exceeds the calculated pre-ablation maximum ongoing dose. Therefore, any first use of a class I or III AAD after day 91 will constitute a failure. Any use of a new class I or III AAD within blanking will lead to a treatment failure at day 91 if the subject does not discontinue the drug prior to the end of the blanking period. Also, treatment failures will occur at day 91 for subjects with increases in AAD dose above the pre-ablation maximum ongoing dose that occur during the blanking period, if the dose is not reduced to or below the pre-ablation maximum before the blanking period ends. Treatment failures occurring after day 90 for increases in AAD dose above the pre-ablation maximum ongoing dose will be set to the date of the adjustment listed in the medication log.

Repeat ablations using radiofrequency (RF) ablation will be counted as chronic treatment failures on the date of the RF ablation, regardless of whether they occur within the 90 day blanking period. Repeat ablations using any energy modality occurring more than 90 days from the index procedure will be counted as chronic treatment failures. Repeat ablations observed through the repeat ablation CRF, as well as repeat ablations observed through the list of 'actions taken' in response to an AE, will both count toward ancillary endpoint #4.

Direct Current Cardioversion (DCCV) cardioversion is not a failure criterion; however, it is noted that when DCCV is observed (through actions taken fields on the Adverse Events CRF, for instance) it is most often performed in response to AF/AFL/AT, which is a failure criterion of ancillary endpoint #4. When a DCCV is observed, the study team should search for documentation of AF/AFL/AT, and the incident will be considered a chronic treatment failure only if the AF/AFL/AT motivating the DCCV is documented.

Analysis Methods

The probability of a subject achieving effectiveness success at 6 months (182 days) will be estimated using survival analysis (the Kaplan-Meier method). The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed.

For every treated subject, day 0 is defined as the day of the index ArcticLine procedure. For subjects without treatment failure through 6 months, those subjects will be censored at the last rhythm monitoring assessment (either in person monitoring at a visit via ECG/Holter, or through ambulatory ECG/transtelephonic monitoring). If a subject without a treatment failure is lost to follow-up, the censoring date will be set to the last date of rhythm monitoring that produced an interpretable rhythm; the date of capture/recording for a rhythm that the core lab was unable to interpret would not count.

For the AF/AT/AFL component of the endpoint, if documentation resulted from rhythm monitoring occurring at the 6-month visit within the 6-month visit window, the date of recurrence will be set to 182

days from the study ablation procedure so that these events will be counted as treatment failures in the 6-month Kaplan-Meier analysis.

Additionally, as stated in the CIP, standard statistics will be used to summarize the percentage of patients without AF/AFL/AT and cumulative time spent in AF/AFL/AT as collected from the 6 month Holter data. Listings will be provided for any data collected relevant to this objective that occurred after 6 months, due to CIP v5 follow-up requirements.

Determination of Subjects for Analysis

- All ArcticLine treated subjects who meet the following criteria will be included in the analysis:
  - o Confirmed acute entrance block of all pulmonary veins
  - o Confirmed acute posterior wall isolation (i.e. roof line and posterior wall line conduction block)
  - o Confirmed acute bi-directional conduction block at the mitral isthmus, if applicable
  - o Confirmed acute bi-directional conduction block at the CTI, if applicable
  - o Available 6 month Holter data (only required for description of Holter times, but not necessary for inclusion in Kaplan-Meier analysis)

7.2.7 Ancillary Objective 5

Estimate the incidence of ArcticLine Catheter-related and ArcticLine cryoablation procedure related serious adverse events (SAE) through the 6 month visit.

Ancillary Endpoint #5

ArcticLine Catheter-related or ArcticLine cryoablation procedure-related SAEs, as adjudicated by the Clinical Events Committee (CEC).

Analysis Methods

The number of SAEs, the number of subjects with SAEs, and the percent of subjects with SAEs will be provided in tabular form. Listings will be provided for any data collected relevant to this objective that occurred after 6 months, due to CIP v5 follow-up requirements.

Determination of Subjects for Analysis

All ArcticLine treated subjects will be included.

7.2.8 Ancillary Objective 6

Characterize procedural data:

- Total procedure time
- Total ArcticLine Catheter use time
- Left atrial dwell time

- Total fluoroscopy time
- Total fluoroscopy time during ArcticLine Catheter use
- Application duration
- Number of applications
- Fluoroscopy dose

Ancillary Endpoint #6

- Total procedure time is defined as time from first venous access to time of last catheter removal.

What was the time of first venous access	FVACCTM_PRSTDTC HH:MM (24 hour clock)
What was the time of last sheath removal	LSHTRTM_PRSTDTC HH:MM (24 hour clock)

- Total ArcticLine Catheter use time is defined as cumulative time from introduction of ArcticLine Catheter into the body to its removal.

What was the time of ArcticLine catheter insertion	ALCTITM_PRSTDTC HH:MM (24 hour clock)
What was the time of ArcticLine catheter removal	ALCTRTM_PRSTDTC HH:MM (24 hour clock)

- Left atrial dwell time is defined as time from transseptal puncture to time of removal of last sheath/catheter from the left atrium.

What was the time of transseptal puncture	TRNSPTM_PRSTDTC HH:MM (24 hour clock)
What was the time of last sheath removal	LSHTRTM_PRSTDTC HH:MM (24 hour clock)

- Total fluoroscopy time is defined as total fluoroscopy time used during the procedure.

What was the fluoroscopy timer at time of first ablation catheter insertion	FFABLTM_PRSTDTC HH:MM:SS
What was the fluoroscopy timer at the end of procedure	FPRENTM_PRSTDTC HH:MM:SS

- Total fluoroscopy time during ArcticLine Catheter use is defined as the cumulative fluoroscopy time from each introduction of ArcticLine Catheter into the body to its removal.

What was the fluoroscopy timer at time of ArcticLine catheter insertion	FACLITM_PRSTDTC HH:MM:SS
What was the fluoroscopy timer at time of ArcticLine catheter removal	FACLRTM_PRSTDTC HH:MM:SS

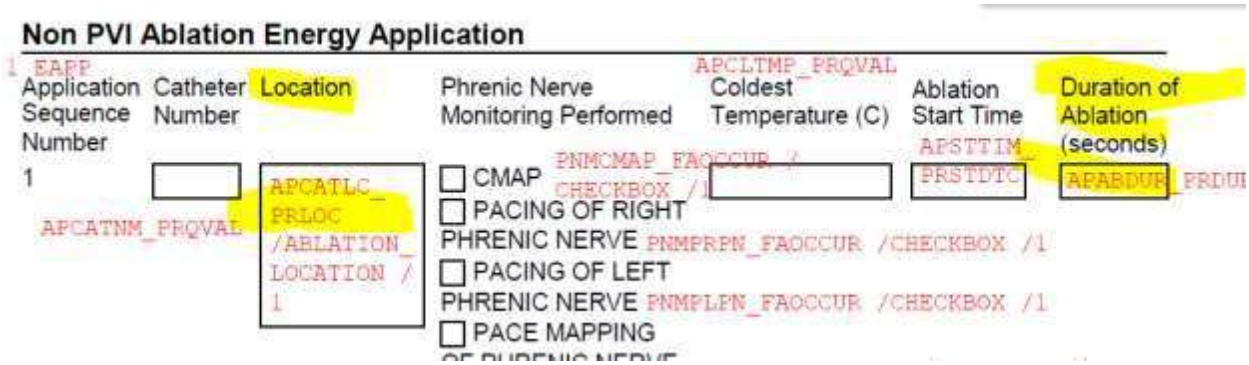
- Application duration is defined as total duration in which cryoablation from the ArcticLine Catheter is applied to cardiac tissue overall and individually to each target area.

• Number of applications is defined as the total number of times in which the ArcticLine Catheter was used to ablate cardiac tissue overall and individually to each target area.

• Total fluoroscopy dose is defined as the amount of radiation deposited into the tissue, measured in Gy or mGy units.

Analysis Methods

The five time metrics (total procedure time, ArcticLine catheter use time, left atrial dwell time, total fluoroscopy time and total fluoroscopy time during ArcticLine use) are calculated as the difference between a single start time and a single end time, as captured in the "Procedure Times" section of the PROCEDURE CRF. At the time of this SAP, the CRF does not allow for the capture of timing for multiple ArcticLine catheter insertions and removals. If multiple ArcticLine insertions and removals occur in an ablation, sites should be instructed to record the first insertion and last removal, and the metric will be calculated from the two CRF fields described above.



Standard statistics (e.g., mean, standard deviation) will be used to summarize each variable. Data from index cryoablations and repeat cryoablations will be reported separately.

Calculation of application duration and number of applications will be calculated from data in the Non-PVI Energy Application CRF where the Catheter number is equal to the row from the subject's Device Identification CRF where the model number is "ArcticLine Catheter (2AL35)". Rows from other catheters (non-Medtronic RF catheters, Freezor MAX) will not be included in these calculations. In the study's final report (which is the primary concern of this SAP), application duration and number of applications will be calculated using all freezes, regardless of duration. However, it is noted that in publications, these metrics may be defined slightly differently: only ArcticLine applications >= 60 seconds in duration may be included in summary statistics, while the rest will be considered as "aborted freezes".

Determination of Subjects for Analysis

All ArcticLine treated subjects will be included.

7.2.9 Ancillary Objective 7

Estimate the incidence of adverse events (AEs) through the 6 month visit.

Ancillary Endpoint #7

Characterize adverse events through the 6 month visit, described as follows:

- Atrioesophageal fistula
- Cardiac perforation/tamponade
- Cerebrovascular accident
- Coronary artery spasm
- Death
- Esophageal injury
- Lung injury (including hemoptysis)
- Major bleeding
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury (ongoing from hospital discharge)
- Pulmonary vein stenosis
- Symptomatic persistent iatrogenic atrial septal defect
- Transient ischemic attack
- Vagal nerve injury
- Vascular access complications

Analysis Methods

The number of AEs, the number of subjects with AEs, and the percent of subjects with AEs will be provided in tabular form. The results of this endpoint may be combined with ancillary endpoint #5 with a column for AEs and a column for SAEs. Listings will be provided for any data collected relevant to this objective that occurred after 6 months, due to CIP v4 follow-up requirements.

Determination of Subjects for Analysis

All ArcticLine treated subjects will be included.

7.3 Center Pooling

The ArcticLine Feasibility study is expected to be conducted at 4 centers in the US and Canada, with a total enrollment of up to 45 subjects to ensure the treatment of at least 15 subjects with the ArcticLine catheter.

The observed rate of the primary endpoint is expected to be low (10% or less, which would lead to an expected outcome of 1 or 2 subjects with primary safety events), so a formal assessment of site-to-site heterogeneity of outcomes in a sample of 15 subjects apportioned between 4 centers is exceedingly

unlikely to detect a difference. As such, any assessment of differences in outcomes between sites and other subgroupings will be qualitative in nature. Data from all sites will be combined without regard to center location for the analysis of the study's endpoints.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Subjects who (A) exit the study prior to completion of a phone conversation or follow-up visit 7 or more days after the index procedure and (B) do not have a primary safety event on or before discharge from the index ablation will be considered as missing for the primary endpoint analysis, on grounds that the assessment of the endpoint is incomplete. Subjects with early exits occurring after the one-week phone call will still be included, however: after 7 days post-index ablation, only the atrioesophageal fistula component, which occurs in less than one in 10,000 cryoballoon ablations[1], counts toward the primary endpoint. Therefore, the likely impact of failing to observe new occurrences of the primary endpoint in subjects not followed past one week is negligible. No effort to statistically impute missing data will be made for the primary endpoint or any ancillary endpoints; all such analyses will be "complete cases" and assume that observed missingness occurs completely at random with respect to the outcome.

7.5 Adjustments for Multiple Comparisons

None of the primary or ancillary objectives from this study require formal hypothesis tests, and thus there is no risk of type I error. Therefore, no adjustments for multiple comparisons will be performed.

7.6 Interim Analyses

An interim analysis will be performed after 15 subjects have been treated with the ArcticLine catheter and had a 1-week follow-up visit. The interim analysis will report on a subset of the study's endpoints including a description of outcomes for the primary objective, as well as ancillary objectives 1 – 3. Descriptions may be by-subject listings, or may follow the methods defined in sections 7.2.2 – 7.2.5, as stakeholders deem appropriate at the time of the report. No hypothesis testing will be performed as part of the analysis of these objectives. There are no predefined criteria for early termination of the trial. Such decisions, if considered, will be made on a qualitative, rather than a statistical, basis. The interim report will also summarize subject disposition, adverse events, protocol deviations, and list ArcticLine procedures and their anatomical targets.

7.7 Subgroup Analysis

A limited number of additional analyses will be performed to evaluate evidence for a differential effect of ArcticLine on the primary endpoint within subgroups of subjects.

At the time of this SAP, current FDA guidance[1] recommends additional evaluation of primary objectives within the following demographic subgroups:

- Age (continuous; calculated as [year of index procedure date – year of birth])
- Gender (captured as male or female by the CRF, with a third level for no response)
- Race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Other, Not Stated)
- Ethnicity (Hispanic or Latino, or not)

Note: As of the writing of version 3 of this SAP, it is known that the final cohort size is 15 subjects, and that the criteria of n≥5 treated subjects per level will not be met for gender, race, or ethnicity, so these analyses will not be performed.

Subgroup analyses will be performed in treated subjects separately for each of the demographic variables listed above for which the following conditions are met:

1) At least two subgroups have n ≥ 5 treated subjects
2) At least 3 primary safety events have been observed.

Exact logistic regression will be used to test for differences in the rate of primary safety events, in a manner consistent with this example SAS code:

```
%let subgroup = Sex;

proc logistic data = primarySafety;
class &subgroup;
model PrimarySafetyEvent (EVENT = 'Yes') = &subgroup;
exact &subgroup;
run;
```

Subgroup analyses will be performed in the same dataset and subjects in which the primary objective is analyzed.

1 https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf

https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf

7.8 Changes to Planned Analysis

Additional details on analysis methods outlined in version 5 of the ArcticLine CIP have been provided in this SAP. Version 3 of this document outlines four changes. First, updates have been made to reflect the new lower sample size of 15 treated subjects that is now expected. Second, the reduced study duration from 12 months to 6 months has been incorporated into the protocol and approved by the FDA and Health Canada. Third, Kapan-Meier analyses have been removed from Ancillary Objectives #5 and #7 because the smaller sample size and reduced duration (6 months vs 12 months) renders this analysis inappropriate. Finally, clarification for having only one planned interim analysis has been made.

Version 2 of the SAP outlined methods for analyzing the expected 20 subjects, which was the expectation at the time of that revision. Further, SAP v2 added clarification on handling "aborted freezes" (applications of ArcticLine < 60 seconds) in the calculation of metrics in Ancillary Objective #6.

Additionally, from version 1 of the SAP, there were three components to the analysis added to this SAP of which the analysis plan in the CIP makes no mention. First, in response to an FDA request, summaries of available data for ancillary objectives 1-3 (assessing acute success of the ArcticLine ablation procedure) will be included in the interim analysis submitted after N=15 subjects have received index cryoablations. Second, in response to Institutional Review Board (IRB) concerns, an analysis is described which investigates the robustness of assumptions involved in treating the primary endpoint as a binomial event. Finally, to better account for early exits and censored data, and to better utilize available information on time to recurrence, a Kaplan-Meier analysis for ancillary objective #4 (chronic treatment success) was outlined.

Analytical deviations from procedures in this SAP may be addressed by the release of newer SAP versions, or will be described in the final report, along with the rationale for the deviation.

8. Validation Requirements

Verification of datasets and analysis of the primary objective will be completed with level I validation (independent programming). Also, the adverse events analysis dataset will be subject to level I validation. Ancillary objectives will be validated with a minimum of level II validation. Analyses that are not related to primary objective or ancillary endpoints will be validated at a minimum of level II validation if being presented externally in an abstract or publication.

9. References

Atrioesophageal fistula formation with cryoballoon ablation is most commonly related to the left inferior pulmonary vein. John RM, Kapur S, Ellenbogen KA, Koneru JN. Heart Rhythm. 2017 Feb;14(2):184-189. doi: 10.1016/j.hrthm.2016.10.018. Epub 2016 Oct 18. PMID: 27769853

U.S. Food and Drug Administration. "FDA Report: Collection, Analysis and Availability of Demographic Subgroup Data for FDA-Approved Medical Products." FDA Web Site. https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf. Published August 2013. Accessed April 28, 2017.

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10. Statistical Appendices

Appendix A. R code and simulation results showing the probability of a subject having a primary safety event at both the index ArcticLine procedure and at a repeat ablation, under the condition that events occurring at index and repeat ablations are independent.

```
## Set initial parameters
N = 15
## Assume that 5% of ArcticLine ablations will result in a primary safety event
indexRate = 0.05
## Assume that 15% of subjects will experience a repeat ablation over 12 months
reablationRate = 0.15
nsims = 100000
set.seed(50819)

indexEvents= matrix(0,ncol = N, nrow = nsims)
repeatEvents = matrix(0,ncol = N, nrow = nsims)
totEvents= matrix(0,ncol = N, nrow = nsims)
two.events = rep(0,nsims)

for (i in 1:nsims){
```

```
indexEvents[i,] = rbinom(N,1,indexRate)
## binomial/independent events assumption:
##  safety events occur at the same rate in repeat ablations compared to index ablations.
## Pr(event at reablation) = Pr(reablation occurs)*Pr(event at any ablation)
repeatEvents[i,] = rbinom(N,1,reablationRate*indexRate)

totEvents[i,]= indexEvents[i,] + repeatEvents[i,]
two.events[i] = ifelse(sum(ifelse(totEvents[i,]==2,1,0))>0,1,0)

}
null.prob= sum(two.events)/nsims
print(null.prob)
[1] 0.00561
```