Medtronic

Clinical Investigation Plan (CIP)

Clinical Investigation Plan/Study Title	FIRE AND ICE – Re-Ablations (retrospective data collection)
Study Product Name	Retrospective Data Collection on re-ablations performed within the FIRE AND ICE Trial. Arctic Front® & Arctic Front Advance® Cardiac CryoAblation Catheter System (Cryo Arm) and NaviStar® ThermoCool® Ablation Catheter (Radiofrequency Arm)
Sponsor/Local Sponsor	Medtronic International Trading Sàrl Route du Molliau 31 CH – 1131 Tolochenaz
Document Version	1.0, 20 Sep 2017
Global Principal Investigator	Prof. Dr. Karl-Heinz Kuck Asklepios Klinik St. Georg Lohmühlenstr. 5 D – 20099 Hamburg, Germany
Scientific Coordinating Investigator	Dr. Alexander Fürnkranz Universitätsklinikum Düsseldorf Moorenstr. 5 D – 40225 Düsseldorf

1. Investigator Statement

Study product Name	Retrospective Data Collection on re-ablations performed within the FIRE AND ICE Trial. Arctic Front® & Arctic Front Advance® Cardiac CryoAblation Catheter System (Cryo Arm) or NaviStar® ThermoCool® Ablation Catheter (Radiofrequency Arm)
Sponsor	Medtronic International Trading Sàrl Route du Molliau 31 CH – 1131 Tolochenaz
Version Number/Date	Version 1.0, 20 Sep 2017

I have read the clinical investigation plan, including all appendices as applicable, and I agree that it contains all necessary details for me and my staff to conduct this retrospective data collection as described. I will conduct this retrospective data collection as outlined herein and will make a reasonable effort to complete the retrospective data collection within the time designated.

I agree to comply with the International Conference on Harmonization Guidelines on Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki (18th World Medical Assembly Helsinki 1964) and all applicable amendments laid down by the World Medical Assemblies and the Data Protection Directive (95/46/EC). I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation/retrospective data collection without the prior written consent of Medtronic.
I will provide all study personnel under my supervision copies of the clinical investigation plan and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the content of this retrospective data collection.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Table of Contents

2. Glossary

Term	Definition
AAD	Antiarrhythmic drugs
AF	Atrial fibrillation
CIP	Clinical Investigation Plan
COV	Close Out Visit
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
DRF	Data Release Form
EC	Ethics Committee
ECG	Electrocardiography
eCRF	Electronic Case Report Form
ERC	Endpoint Review Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LA	Left atrium
PAF	Paroxysmal atrial fibrillation
PI	Principal Investigator
PV	Pulmonary Vein
Re-Do (redo)	Re-Ablation / Re-Ablation procedure
RF	Radiofrequency
RFC	Radiofrequency current
SC	Steering Committee
SDV	Source Data Verification
SIV	Site Initiation Visit

Sponsor Contact Information

Medtronic contact information is provided below. This information is subject to change during the course of the project. Updates to the contact information will be sent to the sites and committees as needed.

Table 2-1: Sponsor contact information

Sponsor Contact	
EU Sponsor Contact **Dr. Ralf Meyer, Director Clinical Research** Medtronic International Trading Sàrl Route du Molliau 31 CH – 1131 Tolochenaz ralf.meyer@medtronic.com +49 175 581 0431	Clinical Study Leader **Petra Kremer, Pr. Clinical Research Specialist** Medtronic GmbH Earl-Bakken-Platz 1 Meerbusch, Germany 40670 petra.Kremer@medtronic.com +49 174 212 2081

CRO Contact Information

Contract Research Organization (CRO) contact information is provided below in Table 2-2. Up to date CRO contact information will be provided to all participating sites within the Investigator Site File (ISF) / Regulatory Binder.

Table 2-2: CRO contact information

Contact Information	Duties Performed
CRO **genae associates nv** Global Headquarters Justitiestraat 6B 2018 Antwerp, Belgium +32 3 290 03 06	The CRO will direct and coordinate the clinical project. Responsibilities include, but are not limited to, monitoring clinical sites, coordinating data collection, including eCRF/database support, and assisting in maintaining compliance to regulations.

3. Synopsis

Title	FIRE AND ICE – Re-Ablations (retrospective data collection)
Clinical Study Type	Retrospective Data Collection on re-ablations performed within the FIRE AND ICE Trial.
Product Name	Products Used within the FIRE AND ICE Trial: Arctic Front® & Arctic Front Advance® Cardiac CryoAblation Catheter System (Cryo Arm; Manufacturer Medtronic, Inc; model number 2AF233 and 2AF283) and NaviStar® ThermoCool® Ablation Catheter (Radiofrequency Arm; Manufacturer Biosense Webster, Inc.)
Sponsor	Medtronic International Trading Sàrl Route du Molliau 31 CH – 1131 Tolochenaz
Indication under investigation	The proposed indication for the Arctic Front Advance® Cardiac CryoAblation Catheter System is as follows: The Arctic Front Advance® Cardiac CryoAblation Catheters are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation (AF). The proposed indications are within the approved indications in Europe for all involved catheter systems.
Investigation Purpose	The FIRE AND ICE Trial collected data to compare efficacy and safety of isolation of the pulmonary veins (PV) using a Cryoballoon catheter versus a radiofrequency ablation with a ThermoCool catheter in patients with drug refractory symptomatic paroxysmal atrial fibrillation (AF). The purpose of this retrospective data collection on re-ablations performed in both treatment arms (Cryo arm and Radiofrequency arm) of the FIRE AND ICE Trial is to gain insight into re-occurrence of atrial arrhythmias resulting in a re-ablation after a performed index ablation procedure. Data to be collected from subject charts include pulmonary vein anatomy, documented atrial arrhythmias prior to re-ablation, pulmonary vein reconnection, pulmonary vein ablation lesion gaps and gap location, ablation lesions performed during the re-ablation, procedure parameters of the RF or cryo catheter utilized during the re-ablation, and success of re-ablations performed. The resulting data may provide insight into the possible causes for re-occurrence of atrial arrhythmias requiring re-ablation.
Product Status	Retrospective Data Collection only on re-ablations performed within

	the FIRE AND ICE Trial (marked products).
Objective(s) and Endpoints	• Summarize the documented atrial arrhythmias prior to re-ablation • Summarize the number of reconnected pulmonary veins • Summarize the number of gaps and location of gaps present in pulmonary vein ablation lesions • Summarize ablation lesion sets created during re-ablation procedure • Summarize acute procedural success of re-ablation procedure • Summarize re-ablation procedure times. • Summarize the length of stay during the hospitalization for re-ablation • Summarize the anti-arrhythmic drug use at time of discharge from the re-ablation procedure. • Summarize adenosine testing
Study Design	Retrospective Data Collection on re-ablations performed within the FIRE AND ICE Trial. No change in the subject population or participating sites. It is estimated to collect the additional retrospective data on re-ablations within 2 months.
Randomization	Not applicable.
Sample Size	No new subjects will be enrolled. In total 119 re-ablations were performed in the FIRE AND ICE Trial. These applicable subjects will be now asked for their consent for the additional data collection on re-ablation procedures.
Inclusion/Exclusion Criteria	Not applicable.
Study Procedures and Assessments	Not applicable. Only data of already performed procedures will be collected.
Safety Assessments	Not applicable. Safety reporting on all events was already performed as part of the FIRE AND ICE Trial.
Statistics	A total of 119 repeat ablations were reported in 110 subjects in the FIRE AND ICE trial. The primary analysis cohort for this CIP will be subjects that provide informed consent for a retrospective data collection (if required by local law / EC). One final analysis will be completed. Data from all consented subjects will be entered into the project database. At the completion of the review by the endpoint review committee, the endpoint review committee classifications will be entered into the database and the database will be frozen. Nine objectives are defined for this CIP as listed above.

4. Introduction

4.1. Background

The FIRE AND ICE Trial was a controlled, prospective, non-inferiority, parallel-group, randomized, interventional, open, blinded outcome assessment (PROBE-Design), multi-centre trial, comparing efficacy and safety of isolation of the pulmonary veins with a Cryoballoon catheter versus a Radiofrequency ablation with a ThermoCool® catheter in subjects with paroxysmal atrial fibrillation[1].

A total of 762 subjects underwent randomization within the FIRE AND ICE Trial: 378 assigned to cryoballoon ablation and 384 assigned to radiofrequency ablation. The mean duration of follow-up was 1.5 years. The primary efficacy endpoint (time to first documented recurrent atrial arrhythmia defined as AF>30s, AT or AFL, AAD prescription or repeat ablation) was reached in 138 subjects in the cryoballoon group and in 143 in the radiofrequency group and the related data published in the New England Journal of Medicine on April 4, 2016[2]. The primary efficacy endpoint was observed to occur at similar rate in the cryoballoon and radiofrequency arms (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority). The secondary analyses on reintervention and rehospitalization showed that subjects treated with cryoballoon as opposed to radiofrequency current (RFC) ablation had significantly fewer repeat ablations (11.8% cryoballoon vs. 17.6% RFC; p=0.03), direct-current cardioversions (3.2% cryoballoon vs. 6.4% RFC; p=0.04), all-cause hospitalizations (32.6% cryoballoon vs. 41.5% RFC; p=0.01), and cardiovascular rehospitalizations (23.8% cryoballoon vs. 35.9% RFC; P=0.01) during follow-up. Additionally, both subject groups (Cryo and RF arm) improved in quality-of-life scores after AF ablation[3].

After the first ablation procedure, in total 119 re-ablations at 15 sites were performed, thereof 49 in the Cryo arm and 70 in the RF arm. The frequency of re-ablation procedures and energy modality of catheter used during the re-ablation was collected during the FIRE AND ICE Trial, but limited data surrounding the re-ablation procedures were collected.

4.2. Purpose

The purpose of this retrospective data collection on re-ablations performed in both treatment arms (Cryo arm and Radiofrequency arm) of the FIRE AND ICE Trial is to gain insight into re-occurrence of atrial arrhythmias resulting in a re-ablation after a performed index ablation procedure. Data to be collected from subject charts include pulmonary vein anatomy, documented atrial arrhythmias prior to re-ablation, pulmonary vein reconnection, pulmonary vein ablation lesion gaps and gap location, ablation lesions performed during the re-ablation, procedure parameters of the RF or cryo catheter utilized during the re-ablation, and success of re-ablations performed. The resulting data may provide insight into the possible causes for re-occurrence of atrial arrhythmias requiring re-ablation.

5. Data to be collected

Administrative Information

- Data Release Form process
- Subject status
- Randomization group assigned within FIRE AND ICE including date of index ablation

Additional data on index ablation

- Data on non-pulmonary vein lesions made
- Cryo Arm (per PV): number of freezes, minimum temperature, duration per freeze, time to effect of freeze, bonus freeze and freeze duration / bonus freeze based on TTE
- RF Arm (per PV): power (watt) minimum, power (watt) maximum, smart touch force measurements (g) minimum, smart touch force measurements (g) maximum and complete RF time (for one side)

Subject characteristics at time of re-ablation and indication for re-ablation

- Date of hospital admission for re-ablation
- Indication for repeat ablation (including symptoms and way of arrhythmia recurrence documentation)
- PV anatomy / stenosis
- Recovered conduction gaps, including localization of gaps and differentiation of gaps (spot gap or linear gap)
- Vein isolation summary pre-ablation / results of PV mapping
- Ablation strategy on PVs chronically isolated
- Membrane-active AADs at time of re-ablation and at discharge after re-ablation
- Anticoagulation at time of re-ablation
- Adenosine use

Procedure parameters

- Rhythm at start of procedure ECG
- Catheters used to perform lesions / energy source used for re-ablation
- Visualization / navigational tools used
- Methods for determining balloon occlusion (Cryo)
- Phrenic nerve monitoring (Cryo Arm)
- Ablation lesions performed
- Cryo Arm (per PV): number of freezes, minimum temperature, duration per freeze, time to effect of freeze and bonus freeze
- RF Arm (per PV): power (watt) minimum, power (watt) maximum, smart touch force measurements (g) minimum, smart touch force measurements (g) maximum and complete RF time (for one side)
- Other lesion sets beyond PVI

Procedure times & procedure summary

- Total procedure times
- Fluoroscopy times and dosage
- LA dwell time
- 3D mapping time
- ACT time (lowest / highest)
- Sedation type
- Cryo Arm: only Arctic Front Advance catheters used / duration of freezes less than planned
- Phrenic nerve injury
- Cardioversion during procedure

Results of re-ablation & discharge

- Success / all targeted PVs isolated / outcome other lesion sets beyond PVI
- Rhythm(s) at end of procedure
- Date of discharge and discharge status (including prolonged hospitalization)
- Re-occurrence of arrhythmia during hospital stay
- Cardioversion after re-ablation due to early AT/AF recurrence
- Membrane-active AADs at time of discharge

6. Objectives and Endpoints

6.1. Objectives and Endpoints

Rationale for study endpoints

Study endpoints have been chosen based on the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[4]. Definitions, mechanisms, and treatment strategies for atrial arrhythmias are outlined in the expert consensus statement. The objectives and endpoints of this data collection reflect these definitions, mechanisms, and treatment strategies. Hospitalization may be the result of a procedural complication, and therefore has been included as an endpoint in this CIP.

6.1.1. Objective: Atrial arrhythmias prior to re-ablation

Summarize the documented atrial arrhythmias prior to re-ablation

Endpoint: Each documented atrial arrhythmia will be classified into one of the following categories:

- Atrial Fibrillation
  - Paroxysmal
  - Persistent
- Atrial Tachycardia
- Atrial Flutter
  - Typical
  - Atypical

6.1.2. Objective: Reconnected pulmonary veins

Summarize the number of reconnected pulmonary veins

Endpoint: Each pulmonary vein will be classified as electrically isolated or not prior to re-ablation. Electrically isolated is defined as bi-directional block, entrance and exit block of PV potentials.

6.1.3. Objective: Number and location of gaps in pulmonary vein ablation lesions

Summarize the number of gaps and location of gaps present in pulmonary vein ablation lesions

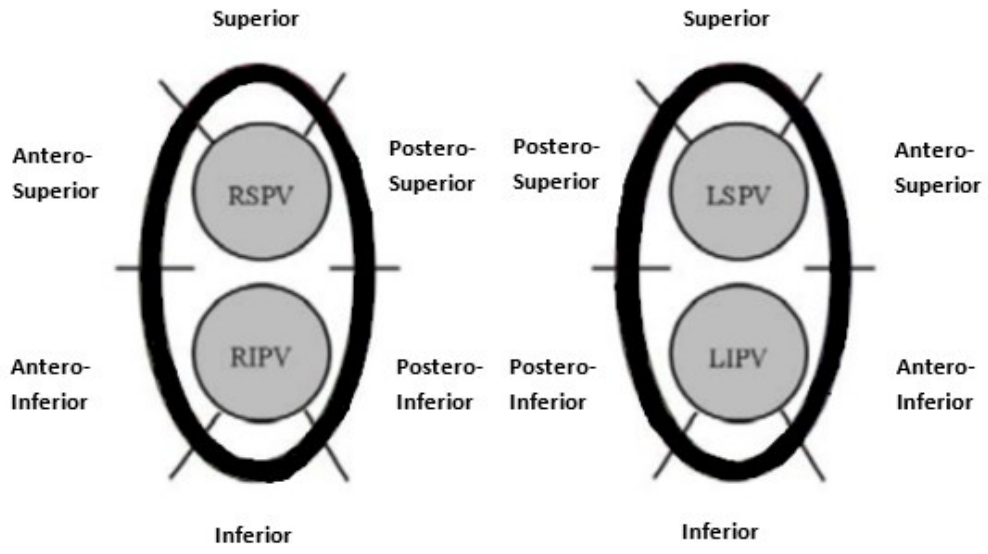
Endpoint: For a redo conducted with a focal catheter and 3D EA mapping, a gap within the pulmonary vein ablation lesion is defined as an electrically reconnected pulmonary vein which after a single spot re-ablation the response to re-ablation is either PV re-isolation or PV activation-sequence change. Ongoing PV conduction after a single spot re-ablation is attributed to an additional gap. Additional gaps are defined similarly.

For a redo conducted with no 3D EA Mapping, gap location may have been estimated utilizing a mapping catheter.

Each gap location will be identified by the classifications provided in Error! Not a valid bookmark self-reference.. To define the location of a gap, including the differentiation for spot gap or linear gap the ipsilateral LA-PV junction is divided into 6 equally distributed segments; superior, antero-superior, antero-inferior, inferior, postero-inferior, and postero-superior.

Spot gap is defined as millimeter size, requiring only a single application without moving the catheter. Linear gap (larger continuous gap) is defined by requiring multiple applications or drawing of the catheter.

Figure 1: Pulmonary Vein Gap Locations



6.1.4. Objective: Ablation lesion sets performed

Summarize ablation lesion sets created during re-ablation procedure.

Endpoint: Each lesion set during re-ablation will be classified into one of the following categories:

- Pulmonary vein isolation (PVI)
- LA AF Trigger
- RA AF Trigger
- Superior vena cava trigger
- Inferior vena cava trigger
- Cavotricuspid Isthmus (CTI)
- Mitral valve isthmus or line
- Left sided roofline
- Complex fractionated atrial electrogram (CFAE)
- Posterior wall
- AVNRT ablation
- other

6.1.5. Objective: Acute procedural success

Summarize acute procedural success as assessed by the sites

Endpoint: Definition of success for each lesion set found below

- Pulmonary vein isolation (PVI)
    - Acute failure is defined as inability to isolate the pulmonary vein (minimally assessed for entrance block and, where assessable, exit block). Acute success is defined as the absence of acute failure.
- LA AF Trigger
    - Acute success is defined as elimination of trigger by ablation procedure.
- RA AF Trigger
    - Acute success is defined as elimination of trigger by ablation procedure.
- Superior vena cava trigger
    - Acute success is defined as elimination of trigger by ablation procedure.
- Inferior vena cava trigger
    - Acute success is defined as elimination of trigger by ablation procedure.
- Cavotricuspid Isthmus (CTI)

- Acute success is defined as bidirectional conduction block at the CTI line

- Mitral valve isthmus ablation
  - Acute success is defined as bidirectional conduction block at the mitral isthmus line
- Left atrial roofline
  - Acute success is defined as confirmed block at the roof line
- Left atrial posterior wall
  - Acute success is defined as confirmed block at the posterior wall
- Complex fractionated atrial electrogram (CFAE)
  - Acute success is defined when ablation of electrograms resulted in termination of atrial fibrillation to sinus rhythm or until all complex fractionated regions were completely eliminated
- AVNRT ablation
  - Acute success is defined as 1) no AVNRT inducibility; 2) no jump; 3) single echo only.
- Other

6.1.6. Objective: Re-ablation procedure times

Summarize re-ablation procedure times.

Endpoint:

1. *Total procedure time* is defined as time from first venous access to time of last sheath removal.
2. *Left atrial dwell time* is defined as time from transseptal puncture to time of removal of last sheath from the left atrium.
3. *Fluoroscopy time* is defined as total fluoroscopy time used during the procedure.

6.1.7. Objective: Re-ablation hospitalization length of stay

Summarize the length of stay during the hospitalization for re-ablation

Endpoint: Length of stay is defined as the number of days from admission to discharge.

6.1.8. Objective: Anti-arrhythmic drug use at re-ablation hospitalization discharge

Summarize the anti-arrhythmic drug use at time of discharge from the re-ablation procedure.

Endpoint: Anti-arrhythmic drug is defined as a Class I or III antiarrhythmic drug

6.1.9. Objective: Summarize adenosine testing

Summarize adenosine testing

Endpoint: Adenosine testing utilized at the time of re-ablation.

7. Study Design

Additional retrospective data collection on data of the performed re-ablations (procedural data) within the FIRE AND ICE Trial in both treatment arms.

The FIRE AND ICE Trial was an investigator initiated, controlled, prospective, non-inferiority, parallel-group, randomized, interventional, open, blinded outcome assessment (PROBE-Design), multi-center trial, comparing efficacy and safety of isolation of the pulmonary veins with a Cryoballoon catheter versus a Radiofrequency ablation with a ThermoCool® catheter in subjects with paroxysmal atrial fibrillation[21].

7.1. Duration

The duration of the data collection for this project is expected to be 2 months, from initiation of first site, data collection, and closing of final site. No subject follow-up is required as the project is retrospective data collection only.

7.2. Rationale

Additional procedural re-ablation data will be collected retrospectively of all enrolled FIRE AND ICE subjects who had a re-ablation procedure during the follow-up period.

Within the FIRE AND ICE Trial, the occurrence of a re-ablation procedure, and the energy modality utilized during the procedure (Cryo or RF) were documented, but limited details on the performed re-ablation procedure were captured. Having additional data surrounding the re-ablation procedures may provide insight into the re-occurrence of atrial arrhythmias resulting in a re-ablation procedure.

8. Product Description (N/A)

Retrospective data collection only. No new assessments will be made nor any products used within this project.

9. Selection of Subjects

9.1. Study Population

No new subjects will be enrolled. Subject population enrolled in the related FIRE AND ICE Trial had drug refractory symptomatic paroxysmal atrial fibrillation with at least two episodes in the last three months prior to the trial enrollment and at least one episode documented. In addition, documented treatment

failure of at least one AAD Type I or III, excluding beta-blocker and AAD intolerance and an age range between 18 and 75 years.

9.2. Subject Enrollment (N/A)

Retrospective data collection only. No new subjects will be enrolled under this CIP.

Prior to any entry of retrospective subject data into the project database, the subject has to sign and date the Data Release Form. A subject is considered as “active subject” within this project at the time the Data Release Form has been fully signed and dated.

The medical files (subject records) at the participating site should indicate that the subject is an active subject within the retrospective data collection.

9.3. Inclusion Criteria (N/A)

No new subjects will be enrolled under this CIP. All subjects of whom the additional re-ablation data will be collected are enrollment and valid subjects within the FIRE AND ICE Trial.

9.4. Exclusion Criteria (N/A)

Not applicable. All subjects of whom the additional re-ablation data will be collected are enrollment and valid subjects within the FIRE AND ICE Trial.

10. Study Procedures

No study procedures will be performed under this CIP. Retrospective data will be collected on performed re-ablations occurred during the FIRE AND ICE follow-up period.

10.1. Schedule of Events (N/A)

Retrospective data collection only. Data on performed re-ablation procedures will be collected that were performed during the follow-up period of the FIRE AND ICE Trial.

10.2. Subject Screening (N/A)

No applicable – no new subjects will be screened or enrolled under this CIP.

10.3. Prior and Concomitant Medications (N/A)

Not applicable as retrospective data collection only.

10.4. Subject Consent (Data Release Form)

A signed and personally dated by the investigator or authorized designee and subject, sponsor and ethics committee (EC) / institutional review board (IRB) approved data release form, written in accordance with the country-specific applicable data privacy acts and the Data Protection Directive (95/46/EC), will be obtained from every subject who had a re-ablation procedure within the FIRE AND ICE Trial prior to the collection of any additional data (if required). Ethical principles as laid down by the Declaration of Helsinki (18th World Medical Assembly, Helsinki 1964) and all applicable amendments laid down by the World Medical Assemblies have been considered for the data release form as well as for the subject consenting process.

The process of obtaining subject data release form by the principal investigator or his/her authorized designee shall:

- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Provide ample time for the subject to read and understand the data release form and to ask questions, receive answers and consider participation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate in the project

The sponsor should avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the retrospective data collection project.

For deceased subjects, in accordance with the country-specific data privacy acts and as approved by the applicable IRB/EC, a relative or legally authorized representative can sign the data release form to collect additional retrospective data as documented in the subject charts. Local IRB/EC procedures must be followed here.

The refusal of a subject (as applicable relative or legally authorized representative) to sign the data release form and therefore not agreeing to the collection of additional retrospective data must never interfere with the subject-physician relationship or future subject treatment.

Should there be any change to this CIP, directly affecting the data privacy of the subject, a modification of the data release form is required. The data release form needs to be signed and personally dated by the investigator or authorized designee and the subject or relative/legally authorized representative (re-consenting if required) after approval by the sponsor and the IRB/EC.

A copy of the fully executed data release form (if required) must be provided to the subject (as applicable to the relative or legally authorized representative) and the original maintained in the trial files / subject files.

10.5. Randomization and Treatment Assignment (N/A)

Not applicable as retrospective data collection only.

Within the FIRE AND ICE Trial the subjects were randomized into two parallel trial groups, namely “Cryo” and “RF”. Randomization was stratified by an age-limit of 65 years, providing the same numbers of treatment assignments per group in both age-cohorts (≤ 65 years versus > 65 years).

10.6. Medication Compliance (N/A)

Not applicable as retrospective data collection only – no medication intake.

10.7. Assessment of Efficacy

Objectives are defined in **section 6.1** for this retrospective data collection.

10.8. Assessment of Safety (N/A)

Not applicable. No new safety data will be collected within this retrospective data collection.

Primary and secondary safety outcome parameter as defined in the FIRE AND ICE Trial CIP were assessed and analyzed accordingly. No additional safety analyses are planned based on the retrospectively collected data on re-ablations procedures.

All devices used in the FIRE AND ICE Trial are marked released. Therefore, Post Marked Surveillance is applicable. The additional procedural data collected within this retrospective data collection will be reviewed for potential product complaints per the project Clinical Safety Management and Potential Complaint Plan and Vigilance reporting to Competent Authorities, if required.

A product complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device that has been placed on the market.

10.9. Recording Data

All data obtained in the context of this retrospective data collection are subject of data protection. This applies to subjects’ data as well as to investigators’ personal data which may be included in any database of Medtronic or the contract research organization (CRO).

The investigators shall take care that any subject documents (e.g. copies of reports or ECGs) transmitted to the database, specific lab or Medtronic contain no names, but only the year of birth and relevant

subject number as generated and assigned to the subject within the FIRE AND ICE Trial (the same numeric identifiers will be used).

All medical data collected within this retrospective data collection will be recorded directly into the eCRFs. Documentation on paper will be restricted to exceptional circumstances only.

It is within the responsibility of the investigator to confirm completeness and correctness of the data entered into the eCRF by signing-off the eCRF (electronic signature).

The data entry into the eCRF will be done by the participating sites. The investigator must ensure to provide the accurate and complete source documents in a timely manner.

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities. Source data are contained in source documents (original records or certified copies).

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic subject records, laboratory notes, memoranda, subject diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, records kept at pharmacy, at the laboratories and the medico technical departments) as involved in this retrospective data collection.

As this is a retrospective data collection only, eCRF cannot be a source document.

10.10. Deviation Handling

The investigator is not allowed to deviate from the CIP. Any deviation to this CIP must be reported in the eCRF regardless of medically justifiable, pre-approved by sponsor (or delegate), an inadvertent occurrence, or taken to protect the subject in an emergency.

A deviation is defined as an event in the project that did not occur according to the CIP or Clinical Trial Agreement (CTA), e.g. deviation in the EC / IRB or Data Release Form process. Prior approval by sponsor (or delegate) is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. inadvertent loss of data due to computer malfunction).

The following data will be collected in the eCRF for deviations:

- Date of deviation
- Visit/template associated with deviation
- Deviation description
- Deviation pre-approved
- Deviation coding

Report of CIP deviations to the EC / IRB should comply with EC / IRB policies and must be reported to the sponsor (or delegate) as soon as possible upon the participating site becoming aware of the deviation.

Sponsor (or delegate) is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training or terminate the project). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and the site, and in some cases, necessitate suspending data entry until the problem is resolved or ultimately terminating the investigator's participation in the project.

The investigator will propose any appropriate modification(s) of the CIP. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

10.11. Subject Withdrawal or Discontinuation

All subjects who had a re-ablation procedure during the follow-up period of the FIRE AND ICE Trial will be asked for their consent to collect the additional retrospective data on the re-ablation procedure. In case a subject withdraw his/her consent for the retrospective data collection after signing the data release form, the withdrawal will be documented with data and reason as applicable. All retrospective data entered in the eCRF by the time of the withdrawal will be used for assessments if not explicitly requested different by the subject. The subjects will be advised within the data release form about their

right to withdraw from the retrospective data collection at any time without statement of reasons and without reprisal.

As there is no follow-up defined for this CIP, there is no impact for withdrawn subjects. Also, as no new subjects will be enrolled under this CIP, replacement of withdrawn subjects is not applicable.

11. Risks and Benefits

11.1. Potential Risks

Retrospective data collection. No direct subject involvement and therefore also no potential risks for the subjects. All primary endpoint data were already collected within the FIRE AND ICE Trial. No potential risks regarding the overall outcomes.

11.2. Potential Benefits

There is no direct benefit for the subject but the additional collected data may help to improve the future treatment of AF subjects.

11.3. Risk-Benefit Rationale

Retrospective data collection only. No direct benefit for the subject is expected but also no risk for the subject.

The additional collected data on the performed re-ablation procedures may help to understand the outcomes after ablations better, as well as on re-occurrence of AF. Both parts may help to improve future treatment of subjects with AF.

12. Data Review Committees

The same Endpoint Review Committee (ERC) will be used under this CIP as for the FIRE AND ICE Trial. There will be three assigned members of the ERC as listed in **Appendix IV** who are experienced clinicians, not related to the project and will be blinded to the therapy group.

The ERC members will centrally review and adjudicate the collected data on re-ablations, e.g. gap assessment, ablation type performed, and re-ablation success as required.

The Lead Principal Investigator as well as the Scientific Coordinating Investigator will provide advice on the scientific and clinical aspects of the CIP and related documents, as well as scientific and clinical

advice on the execution and scientific reporting of the retrospective data collection. No additional Steering Committee will be involved under this CIP.

No DSMB will be involved in this project as no safety data will be collected in addition under this CIP.

13. Statistical Design and Methods

13.1. General Considerations

A total of 119 repeat ablations were reported in 110 subjects in the FIRE AND ICE Trial. The primary analysis cohort for this CIP will be subjects that provide informed consent for a retrospective data collection (as required). Of the 110 subjects with re-ablations during the FIRE AND ICE Trial, only those that consent for retrospective data collection will be included in analyses (as required by local law / EC).

The Statistical Analysis Plan (SAP) will be created prior to data analysis and include a comprehensive description of the statistical methods to be included in study reports. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report. Medtronic employees or their designated representatives will perform all statistical analyses.

13.2. Analysis Timing

One final analysis will be completed. Data from all consented subjects will be entered into the project database. At the completion of the review by the endpoint review committee, the endpoint review committee classifications will be entered into the database and the database will be frozen. Analyses comparing randomization arms will not be conducted until after the database is frozen.

13.3. Objectives

13.3.1. Objective #1: Atrial arrhythmias prior to re-ablation

Summarize the documented atrial arrhythmias prior to re-ablation

Endpoint Definition

Each documented atrial arrhythmia will be classified into one of the following categories:

- Atrial Fibrillation
  - Paroxysmal
  - Persistent

- Atrial Tachycardia
- Atrial Flutter
  - Typical
  - Atypical
- Other

Analysis methods

The first re-ablation for each subject will be used for analysis. Each first re-ablation will be grouped into the following categories:

1. atrial fibrillation (paroxysmal)
2. atrial fibrillation (persistent)
3. atrial flutter or atrial tachycardia
4. other

The percent of subjects by indication for re-ablation will be summarized. The distribution of type of arrhythmia will be compared between randomization arms using exact methods.

13.3.2. Objective #2: Reconnected pulmonary veins

Summarize the number of reconnected pulmonary veins

Endpoint Definition

Each pulmonary vein will be classified as electrically isolated or not prior to re-ablation. Electrically isolated is defined as bi-directional block, entrance and exit block of PV potentials.

Analysis Methods

The first re-ablation for each subject will be used for analysis. The number of electrically isolated pulmonary veins will be assessed for each subject and the number of PVs isolated will be compared between randomization arms using a two-sample t-test. It is anticipated that the majority of subjects will have four major pulmonary veins; LIPV, LSPV, RIPV, and RSPV. If a subject has an anatomy in which electrical isolation of more or less than the four major PVs are tested, the number of electrically isolated pulmonary veins for that subject will be normalized to 4.

13.3.3. Objective #3: Number and location of gaps in pulmonary vein ablation lesions

Summarize the number and location of gaps in pulmonary vein ablation lesions

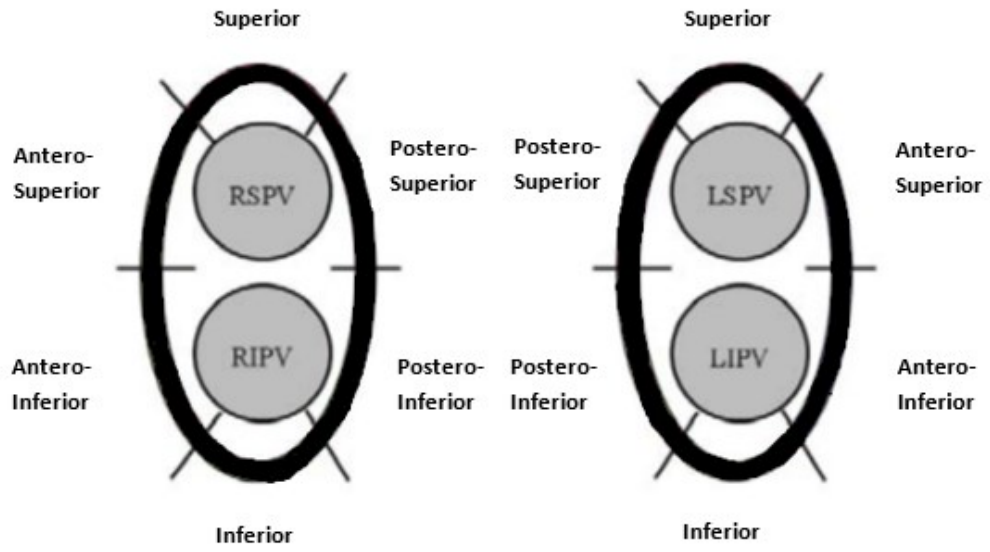
Endpoint: For a redo conducted with a focal catheter and 3D EA mapping, a gap within the pulmonary vein ablation lesion is defined as an electrically reconnected pulmonary vein which after a single spot re-ablation the response to re-ablation is either PV re-isolation or PV activation-sequence change. Ongoing PV conduction after a single spot re-ablation is attributed to an additional gap. Additional gaps are defined similarly.

For a redo conducted with no 3D EA Mapping, gap location may have been estimated utilizing a mapping catheter.

Each gap location will be identified by the classifications provided in **Figure 2**. To define the location of a gap, including the differentiation for spot gap or linear gap, the ipsilateral LA-PV junction is divided into 6 equally distributed segments; superior, antero-superior, antero-inferior, inferior, postero-inferior, and postero-superior.

Spot gap is defined as millimeter size, requiring only a single application without moving the catheter. Linear gap (larger continuous gap) is defined by requiring multiple applications or drawing of the catheter.

Figure 2: Pulmonary Vein Gap Locations



Analysis methods

The number and location of gaps will be presented using summary statistics.

13.3.4. Objective #4: Ablation lesion sets performed

Summarize ablation lesion sets created during re-ablation procedure.

Endpoint Definition

Each lesion set during re-ablation will be classified into one of the following categories:

- Pulmonary vein isolation (PVI)
- LA AF Trigger
- RA AF Trigger
- Superior vena cava trigger
- Inferior vena cava trigger

- Cavotricuspid Isthmus (CTI)
- Mitral valve isthmus or line
- Left sided roofline
- Complex fractionated atrial electrogram (CFAE)
- Posterior wall
- AVNRT ablation
- Other

Analysis methods

The first re-ablation for each subject will be used for analysis. The number of lesion sets for each subject will be counted. If a subject has multiple PVs ablated, each PV will count as a lesion set towards the subjects total count. The number of lesion sets will be compared between randomization arms using a two-sample t-test.

13.3.5. Objective #5: Acute procedural success

Summarize acute procedural success as assessed by the sites.

Endpoint Definition:

Definition of success for each lesion set found below

- Pulmonary vein isolation (PVI)
  - Acute failure is defined as inability to isolate the pulmonary vein (minimally assessed for entrance block and, where assessable, exit block). Acute success is defined as the absence of acute failure.
- LA AF Trigger
  - Acute success is defined as elimination of trigger by ablation procedure.
- RA AF Trigger
  - Acute success is defined as elimination of trigger by ablation procedure.
- Superior vena cava trigger
  - Acute success is defined as elimination of trigger by ablation procedure.
- Inferior vena cava trigger
  - Acute success is defined as elimination of trigger by ablation procedure.
- Cavotricuspid Isthmus (CTI)
  - Acute success is defined as bidirectional conduction block at the CTI line
- Mitral valve isthmus ablation
  - Acute success is defined as bidirectional conduction block at the mitral isthmus line
- Left atrial roofline
  - Acute success is defined as confirmed block at the roof line

- Left atrial posterior wall
    - Acute success is defined as confirmed block at the posterior wall
- Complex fractionated atrial electrogram (CFAE)
    - Acute success is defined when ablation of electrograms resulted in termination of atrial fibrillation to sinus rhythm or until all complex fractionated regions were completely eliminated
- AVNRT ablation
    - Acute success is defined as 1) no AVNRT inducibility; 2) no jump; 3) single echo only.
- Other

Analysis methods

The first re-ablation for each subject will be used for analysis. For subjects receiving only re-isolation of pulmonary veins, acute procedural success is defined as minimally assessed for entrance block, and where assessable, exit block. For subjects receiving additional lesions beyond PVI, acute success is defined as successful PVI plus successful ablations as defined in the endpoint definition for all ablations.

Each subject will be classified as an acute procedural success or not. Acute procedural success will be compared between randomization arms using exact methods.

13.3.6. Objective #6: Re-ablation procedure times

Summarize re-ablation procedure times.

Endpoint:

1. *Total procedure time* is defined as time from first venous access to time of last sheath removal.
2. *Left atrial dwell time* is defined as time from transseptal puncture to time of removal of last sheath from the left atrium.
3. *Fluoroscopy time* is defined as total fluoroscopy time used during the procedure.

Ablation methods

The first re-ablation for each subject will be used for analysis. Procedural times will be compared between randomization arms with a two-sample t-test. Separate t-tests will be used for each procedure time metric.

13.3.7. Objective #7: Hospitalization length of stay

Summarize the length of stay during the hospitalization for re-ablation

Endpoint Definition

Length of stay is defined as the number of days from admission to discharge.

Analysis Methods

The first re-ablation for each subject will be used for analysis. Hospital length of stay will be compared between randomization arms with a two-sample t-test. If the distribution of length of stay is skewed non-normal, a non-parametric Wilcoxon test will be utilized.

13.3.8. Objective #8: Anti-arrhythmic drug use at discharge

Summarize the anti-arrhythmic drug use at time of discharge from the re-ablation procedure.

Endpoint Definition

Anti-arrhythmic drug is defined as a Class I or III antiarrhythmic drug prescribed at discharge.

Analysis Methods

The first re-ablation for each subject will be used for analysis. The percent of subjects discharged from re-ablation on anti-arrhythmic drugs will be compared between randomization arms using exact methods.

13.3.9. Objective #9: Adenosine testing

Summarize adenosine testing utilized during re-ablation procedure.

Endpoint Definition

Use of adenosine testing during re-ablation.

Analysis Methods

The first re-ablation for each subject will be used for analysis. The percent of subjects with adenosine testing will be compared between randomization arms using binomial exact methods.

14. Ethics

14.1. Statement(s) of Compliance

This retrospective data collection will be conducted in accordance with the clinical investigation plan, the International Conference on Harmonization Guidelines (ICH) on Good Clinical Practice (GCP) the Data Protection Directive (95/46/EC) as well as all applicable country-specific data protection regulations and the ethical principles that have their origin in the Declaration of Helsinki (18th World Medical Assembly, Helsinki 1964) and all applicable amendments laid down by the World Medical Assemblies. The principles of the Declaration of Helsinki have been implemented through adherence to accepting scientific principles, the subject Data Release Form process, EC / IRB approval, project training, clinical trial registration, risk-benefit assessment and publication policy. No vulnerable subject groups were included in the FIRE AND ICE Trial.

Due to the set-up of this project, being a retrospective data collection (focused on re-ablation data) in addition to the data already collected within the FIRE AND ICE Trial, full compliance to ICH GCP is not given due to not applicable elements for this type of project.

Before initiating any sites in any country for the retrospective data collection, approval/notification of the relevant EC / IRB and/or competent authority will be obtained as appropriate per local regulations.

In case any action is taken by an EC / IRB with respect to this retrospective data collection, the sponsor should be informed immediately about the action taken (via the investigator or the assigned CRA).

15. Study Administration

15.1. Monitoring

Authorized, qualified clinical research associates (CRAs) of the CRO (genae associates nv with global headquarters at Justitiestraat 6B, 2018 Antwerp, Belgium) will accomplish the monitoring of the collected retrospective data per the project specific monitoring plan. Remote monitoring is also accepted for this CIP. No sponsor monitors will be involved for this retrospective data collection.

Assignment of the genae CRAs per participating site is documented in the project specific monitoring plan.

All sites to be initiated for this retrospective data collection were active enrolling hospitals within the FIRE AND ICE Trial and therefore already experienced regarding the content of this additional data collection. Site Initiation Visits (SIVs) under this CIP may be conducted via phone. The SIV (via on-site visit or phone) can take place when the clinical trial agreement is fully executed, confidentiality agreement is fully executed, ethics approval is obtained (as applicable), competent authority requirements are fulfilled (as applicable), signed and dated CV of the principal investigator is available, approved data release form and sponsor approval/request to conduct the SIV.

COVs will be conducted either via a visit (may be a combined visit with the last monitoring visit) or by phone as soon as the additional data collection is completed. There will be no data collection after that time.

It is important that the investigator and relevant site personnel are available during the monitoring visits and that appropriate location, internet access and enough time is devoted to the process. Access to all applicable source documents as defined in Section 10.9 Recording Data needs to be ensured for the CRA. A personal computer with internet access should be available to the CRA for all data stored in the data system of the hospital or catheter lab as applicable.

The main duty of the contracted genae CRA is to help Medtronic and investigator to maintain a high level of data and regulatory quality in all aspects of the retrospective data collection. For this purpose, the CRA will verify on site all signed data release forms (100%) as well as conducting verification on data entered into the eCRF as defined in the monitoring plan (SDV – Source Data Verification). Within the project specific monitoring plan the extent of SDV is defined, such as 100% SDV on key data for the defined objectives, 10% SDV for e.g. medication data and data items to be only checked for completeness.

15.2. Data Management

The data management and statistical analysis plan defines the procedures for data review, database cleaning and issuing and resolving data queries as well as the procedures for verification, validation and securing of electronic clinical data systems if applicable.

Data will be collected using an electronic data management system for clinical studies. eCRF data will be stored in a secure, password-protected database. Data will be reviewed using programmed and manual data checks. Data queries will be made available to participating sites for resolution. Project management reports may be generated to assess data quality and data entry progress. At the end of the project, the data will be frozen and will be retained indefinitely by Medtronic. All records and other information about subjects participating in the project will be treated as confidential.

15.3. Direct Access to Source Data/Documents

The investigator agrees that representatives or the designee of Medtronic such as CRAs and auditors, and appropriate Regulatory Agencies will be given direct access to the regular clinical files of the subject.

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important for this retrospective data collection. Any party with direct access should take all reasonable precautions within this constraint of the applicable regulatory requirements to maintain the confidentiality of subject identities and Medtronic proprietary information.

Quality assurance is defined as the planned and systematic actions that are established to ensure that the retrospective data collection is performed and the documented data collected in compliance with GCP and the applicable regulatory requirements.

The investigator should permit in addition to the regular monitoring and EC/IRB reviews, also auditing by or on behalf of Medtronic and inspection by applicable regulatory authorities. The investigator shall take appropriate measures required by Medtronic to take corrective actions for all problems found during the audit or inspections.

15.4. Confidentiality

General

All information disclosed or provided by Medtronic (or any company / institution acting on his behalf), or collected during the retrospective data collection, including, but not limited to, the clinical investigation plan, the eCRFs and the results/data obtained, is confidential. The investigator or any person under his / her authority agrees to undertake to keep confidential and not do disclose the information to any third party without the prior written approval of Medtronic. Co-Investigators as applicable shall be bound by the same obligations as the investigator. The investigator shall inform the co-investigators of the confidential nature of this project as applicable. Both, the investigator and the co-investigators shall use the information solely for the purpose of the project, to the exclusion of any use for their own or for a third party's account.

Subject privacy

All subject data collected under this CIP will be handled strictly confidential and pseudonymized, no names or initials will be used, but only a numeric code and possibly the data of the year of birth. The same subject identifiers will be used as for the FIRE AND ICE Trial to ensure the correct merge of both data sets for the analyses. All analyses performed will be made on pseudonymized data only. Also all results published based on this retrospective data collection will be without disclosing confidential subject data.

All subject data will be protected against unauthorized access and a decryption takes place only under the conditions by the country-specific law.

15.5. Liability (N/A)

Retrospective data collection only without direct subject involvement.

15.6. CIP Amendments

Approval of amendments to the CIP are required are required at each participating site from the following groups prior to implementation of the revised CIP at the participating site:

- Medtronic
- Principal Investigator (where required by local law)
- Competent / Regulatory Authority (if regulatory approval is required)
- Central IRB / EC

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB / ECs as required by the local committee.

In some instances, an amendment may require a change in the data release form. In this case, the investigator must receive an EC / IRB approval / favorable opinion concerning the revised data release form prior to implementation of the change.

15.7. Record Retention

The investigator must maintain confidential all project documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator must retain the related documents at least five year after the completion or discontinuation of this retrospective data collection or longer if required by national legislation. This includes, but is not limited to the following documents:

- Signed CIP and amendments (as applicable)
- Issued regulatory approvals (communication with regulatory authorities / ECs)
- Clinical Trial Agreement
- Signed Data Release Forms
- Subject Identification Listings
- Site team authorizations including training documentation and qualification documentation
- CRF pages
- Lab- and medical files
- Site Close Out Report
- Relevant project communication, including as applicable audit and inspection documentation
- Project reports / final project report

The investigator must notify Medtronic prior to destroying any essential project documents within the specified period following completion or discontinuation of the project.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at genae (CRO) during the course the project. Document transfer from genae to Medtronic is part of the defined CRO project closing activities.

After closure of the project Medtronic will archive records and reports indefinitely.

15.8. Publication and Use of Information

Publications from the FIRE AND ICE Re-Ablations retrospective data collection will be handled according to Medtronic Global Standard Operating Procedures and as indicated in the Clinical Trial Agreement (CTA).

The publication rules are regulated separately and described in detail in a publication plan that is confirmed by the publication committee. The overall process and content of the publication plan is comparable with the FIRE AND ICE Trial. Registering and posting the project results on ClinicalTrials.gov will be done based on the posting rules stipulated.

Medtronic will be responsible for preparing any reports based on the additional retrospective data collection. A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRBs/ECs and CAs of participating countries when required by local law.

An individual site's study data will be made accessible to the corresponding investigator after the completion of the project, if requested.

All information and documents provided by Medtronic or its representatives are and remain the sole property of Medtronic. The investigator shall not mention any information for any other intellectual property rights.

All results, data and documents, which arise directly or indirectly from this project in any form, shall be the immediate and exclusive property of Medtronic.

Publication Committee

Medtronic will form the FIRE AND ICE Re-Ablations Publication Committee (refer to **Appendix V**). Medtronic personnel may serve as members of the committee. This committee will manage publications with the goal of publishing findings from the data. The publication committee will develop the publication plan as a separate document.

The publication committee's role is to 1) manage and develop elements addressed in the publication plan, 2) execute the publication plan, 3) oversee the publication of primary, secondary and ancillary study results as applicable, 4) review and prioritize publication proposals, 5) provide input on publication content, and 6) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the publication plan.

Membership in the publication committee does not guarantee authorship. The committee will meet as needed.

15.9. Suspension or Early Termination

Early termination is the closure of a clinical study/project that occurs prior to meeting defined endpoints or objectives. This is possible for the whole study/project or a single participating site. Suspension is a temporary postponement of study/project activities related to enrollment. This is possible for the whole study/project or a single participating site. If suspension is lifted, the investigator shall assess whether or not to continue the clinical study/project at their site.

Possible reasons for considering suspension or termination of this retrospective data collection include but are not limited to:

- Decision by Medtronic or competent authority

Possible reasons for investigator or participating site termination or suspension include but are not limited to:

- Persistent non-compliance to the CIP (e.g. lack of data entry)
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- IRB/EC suspension of the participating site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the retrospective data collection)

Procedures Medtronic-initiated / Regulatory-initiated termination or suspension

- Medtronic will promptly inform the investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- The investigator will promptly inform the IRB/EC of project termination or suspension
- In the case of project termination, the investigator must inform the subjects; information of the personal physician of the subjects to ensure appropriate care and follow-up is not required, as this is a retrospective data collection only
- In the case of a study suspension, entry of new subject data must stop until the suspension is lifted by Medtronic
- No new assessments or follow-up are part of this retrospective data collection; therefore, no direct impact on the patient care and welfare

Procedures Investigator-initiated termination or suspension

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension.
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities (where required per regulatory requirements)
- The investigator will promptly inform the subjects
- No new assessments or follow-up are part of this retrospective data collection; therefore, no direct impact on the patient care and welfare

Procedures IRB/EC-initiated termination or suspension

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Entry of new data sets in the database must stop until the suspension is lifted
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects with the rationale for the project termination or suspension
- The investigator will promptly inform the regulatory authorities (where required per regulatory requirements)
- No new assessments or follow-up are part of this retrospective data collection; therefore, no direct impact on the patient care and welfare

16. References

1. Fürnkranz A, Brugada J, Albenque JP, Tondo C, Bestehorn K, Wegscheider K, Ouyang F, Kuck KH. Rationale and Design of FIRE AND ICE: a multicenter randomized trial comparing efficacy and safety of pulmonary vein isolation using a cryoballoon versus radiofrequency ablation with 3D-reconstruction. J Cardiovasc Electrophysiol 2014;25:1314-1320
2. Karl-Heinz Kuck, M.D., Joseph Brugada, M.D., Alexander Fürnkranz, M.D., Andreas Metzner, M.D., Feifan Ouyang, M.D., K.R. Julian Chun, M.D., Arif Elvan, M.D., Ph.D, Thomas Arentz, M.D., Kurt Bestehorn, M.D., Stuart J. Pocock, Ph.D., Jean-Paul Albenque, M.D., Ph.D., and Claudio Tondo, M.D., Ph.D., for the FIRE AND ICE Investigators: Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N Engl J Med 2016;374:2235-2245
3. Karl-Heinz Kuck, Alexander Fürnkranz, K.R. Julian Chung, Andreas Metzner, Feifan Ouyang, Michael Schlüter, Arif Elvan, Hae W. Lim, Fred J. Kueffer, Thomas Arentz, Jean-Paul Albenque, Claudio Tondo, Michael Kühne, Christian Sticherling, and Joseph Brugada, on behalf of the FIRE AND ICE Investigators: Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. European Heart Journal doi:10.1093/eurheartj/ehw285.
4. Calkins H, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Heart Rhythm. 2012; 9(4): p. 632-696

5. Appendices

Appendix I – List of Participating Countries
Appendix II – List of Participating Sites and Investigators
Appendix III – Data Release Form (DRF)
Appendix IV – Members of Endpoint Review Committee (ERC)
Appendix V – Members of Publication Committee

6. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Petra Kremer, Pr. Clinical Research Specialist Fred Kueffer, Sr. Pr. Statistician

Appendix I – List of Participating Countries

(sorted in alphabetical order)

Country

Czech Republic
France
Germany
Hungary
Netherlands
Spain
Switzerland

Appendix II – List of Participating Clinical Sites and Investigators

(sorted in alphabetical order by participating country)

Any changes to this committee will be provided under separate cover as needed.

Country	Site	Principal Investigator
Czech Republic	Nemocnice Na Homolce Praha Roentgenova 2, 150 30 Praha 5	Prof. Dr. Petr Neuzil Head of Department of Cardiology
France	Clinique Pasteur Toulouse 43, avenue de Lombez BP 27617, F-31076 Toulouse Cedex 3	Dr. Jean-Paul Albenque Cardiologist / Department de Rythmologie
Germany	Asklepios Klinik St. Georg Hamburg Lohmühlenstr. 5, 20099 Hamburg	Prof. Dr. Karl-Heinz Kuck Head of Department of Cardiology
	Cardioangiologisches Centrum Bethanien CCB, Frankfurt Wilhelm-Epstein-Str. 4, 60431 Frankfurt	PD Dr. KR Julian Chun Doctor of Cardiology
	Universitätsmedizin Greifswald Ferdinand-Sauerbruch-Straße, 17475 Greifswald	Dr. Mathias C. Busch Oberarzt Kardiologie / senior physician
	Herz-Zentrum Bad Krozingen Südring 15, 79189 Bad Krozingen	Prof. Dr. Thomas Arentz Chefarzt Rhythmologie / chief physician
	Klinikum Bad Neustadt Salzburger Leite 1, 97616 Bad Neustadt	Prof. Dr. Thomas Deneke Leiter der Klinik für Kardiologie II / Head of Cardiology
	Herz-Zentrum Bodensee Luisenstraße 9a, 78464 Konstanz	Prof. Dr. Volker Kühlkamp Chefarzt Elektrophysiologie / Head of electrophysiology
Hungary	Semmelweis Egyetem Budapest	Dr. László Alajos Gellér

	Üllöi út 26, H-1085 Budapest	Cardiologist
Netherlands	Isala Klinieken Zwolle Dokter van Heesweg 2, 8025 AB Zwolle	Dr. Arif Elvan Cardiologist
Spain	Hospital Clinic de Barcelona Carrer de Villarroel, 170, Escala 3, Planta 6, 08036 Barcelona	Dr. Josep Lluís Mont Girbau Cardiologist / Head of Arrhythmia Section
	Hospital Clínico Universitario "Virgen de la Victoria" Malaga Campus Universitario de Teatinus s/n, 29010 Málaga	Dr. Alberto Barrera Cordero Cardiologist
	Hospital Clinico Universitario Valencia Avenida Blasco IBA#EZ 17, 46010 Valencia	Dr. Ricardo Ruiz-Granell Cardiologist / Electrophysiologist
	Hospital Clinico San Carlos Madrid Professor Martín Lagos, S/N, 28040 Madrid	Dr. Nicasio Pérez Castellano Cardiologist
Switzerland	Universitätsspital Basel Petersgraben 4, CH-4031 Basel	PD Dr. Michael Kühne Leiter Vorhofflimmerklinik /Head of AF department

Appendix III – Data Release Form (Master Version)

INFORMATION SHEET

Investigator and Sponsor

Study	FIRE AND ICE RE-Ablations
Sponsor	Medtronic International Trading Sàrl Route du Molliau 31 1131 Tolochenaz Switzerland
Site	*<Insert site name>*
Investigator	*<Insert name and title of the site Principal Investigator (PI)>*

This study is a multi-center Non-Interventional Post-Market study to collect retrospective data on re-ablation procedures performed during the Follow-Up period of the FIRE AND ICE study.

PURPOSE OF THE STUDY:

The purpose of this study is to collect procedural data of performed re-ablation procedures in patients with re-current atrial fibrillation after a performed ablation procedure, treated either with a cryoballoon ablation or a radiofrequency ablation. These data are collected for medical research purposes to gather information on products (ablation catheters) and their performance during and after the current study.

You (and about 115 other patients) are invited to take part in this study, because you were a participant in the Fire and Ice study and were diagnosed with recurrent atrial fibrillation after the performed study ablation procedure and you have been treated with a re-ablation procedure by your doctor. The data of this re-ablation procedure was not collected during the initial Fire and Ice study, but is now of interest for this study.

USE OF PERSONAL DATA/CONFIDENTIALITY:

Your participation in this study is entirely voluntary and confidential.

While participating in this study the following personal data will be collected:

- identifying data (name, age, address) <
- medical and health data from your medical records incl. data about your treatment, especially the atrial fibrillation procedure and your medication

(hereinafter "**personal data**")

Your personal data will be processed at all times in accordance with applicable legal requirements.

In general only the study doctor and/or nurse as well as the study monitor who acts on behalf of Medtronic and other designated parties that are involved in the study have direct access to your personal data in your medical file. Furthermore it may happen, that members of the ethical committee and representatives of national, European or other international public authorities are granted direct access to your personal data in order to comply with legal requirements.

For conducting the study your personal data will be transferred to and processed by Medtronic (meaning Medtronic, Inc. as well as all affiliates of this group of companies) or a third party designated by Medtronic **– but solely in a key coded form**. Key coded form means that your name, date of birth, contact information, and any other information that might disclose your identity, will be replaced by a Patient Identification number (Patient ID). Only this Patient ID will be used on the study documents and reports. The key between this Patient ID and your identity will be kept on site by the study staff team.

Your key coded personal data will be transferred to Medtronic or a third party designated by Medtronic which is located in the country where you are treated or in a other member state of the European Economic Area but maybe also in the United States or another country where the European Directive on Data Protection does not apply.

Medtronic may also use your coded personal data for additional purposes such as overseeing and improving the performance of its device, new medical research, developing new medical products or procedures, and other business purposes.

You are entitled to access the personal data collected about you and to have inaccuracies corrected.

Any published information including reports and articles about the study will not include your name or any information that could personally identify you. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

If you agree upon, your personal physician will be informed about your participation in the study.

SIGNATURE SHEET

(ISO 14155: 2011 4.7.5)

I have read the patient information of this study and my study doctor has answered all my questions regarding the study.

I had sufficient time to consider my participation into this study, I am aware that participation into this study is completely voluntary, and I agree to follow the instructions from the study doctor.

I realize that I may decide to refuse participation or stop participation at any time without penalty and without affecting the quality of my health care or the relationship with my study doctor.

I understand and agree that personal information about me will be collected from my medical records, used and processed (manually and by computer) by the manufacturer of a medical device used in my treatment or any other designated party that is involved in the study (e.g. hospital, study doctor, regulatory authorities, ethics committees).

I understand and agree that representatives from Medtronic, regulatory authorities and the Ethics Committee representatives will be granted direct access to my medical records.

I understand and agree that the study doctor(s)/hospital will release the relevant personal information about me for the purpose of this study.

I understand that I am entitled to access the personal information collected about me and to have inaccuracies corrected.

I agree to participate voluntarily in and comply with this study.

I understand that I will receive a dated and signed copy of the Data Release Form.

- *This notification can be deleted for countries where personal physicians do not exist*
- *Use if EC requires a checkbox*

It is your choice if you would like your personal physician to be informed of your participation in this study. Please, check one of the boxes to show your choice:

! must be checked by patient

☐ I agree that my personal physician is informed about my participation in this study.
☐ I disagree that my personal physician is informed about my participation in this study.

Patient:

Name	Signature ! must be written by patient	Date (dd MMM yyyy) ! must be written by patient

Legal Representative if patient is unable to give consent:

Name	Signature ! must be written by Legal Representative	Date (dd MMM yyyy) ! must be written by Legal Representative

Study doctor or designated person by study doctor:

I have conducted the informed consent discussion.

! Only persons officially trained and authorized on the delegated task list are allowed to sign off

Name	Signature	Date (dd MMM yyyy)

If patient, or patient's legally acceptable representative, is unable to read:

I have attended the entire Data Release discussion. I attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative. Data Release consent was freely given by the patient or the patient's legally acceptable representative.

Impartial Witness:

Name	Signature ! must be written by Impartial Witness	Date (dd MMM yyyy) ! must be written by Impartial Witness

Appendix IV – Members of Endpoint Review Committee (ERC)

(sorted in alphabetical order)

Any changes to this committee will be provided under separate cover as needed.

Member Name	Institution
Dr. Malte Kuniss	Kerckhoff Klinik Bad Nauheim Benekestr. 2-8 D-61231 Bad Nauheim
Prof. Dr. Thorsten Lewalter	Peter Osypka Herzzentrum Am Isar-Kanal 36 D-81379 München, Germany
Prof. Dr. Lars Lickfett	Gemeinschaftspraxis für Kardiologie und Pneumologie Mönchengladbach Ludwig Weber Straße 15 D-41061 Mönchengladbach

Appendix V – Members of Publication Committee

(voting members are sorted in alphabetical order)

Any changes to this committee will be provided under separate cover as needed.

Member Name	Institution
Dr. Jean-Paul Albenque	Clinique Pasteur 45 avenue de Lombez BP 27617 31076 Toulouse Cedex 3, France
Prof. Dr. Josep Brugada (Co-Chairman)	Hospital Clinic, University of Barcelona Villarroel 170, 08036 Barcelona, Spain
Prof. Dr. Karl-Heinz Kuck (Chairman)	Asklepios Klinik St. Georg Lohmühlenstr. 5 D-20099 Hamburg, Germany
Prof. Dr. Claudio Tondo	Cardiac Arrhythmia Research Centre Department of Cardiovascular Medicine Centro Cardiologico Monzino University of Milan Via Parea 4 20138 Milan, Italy
Fred Kueffer (Medtronic member)	Medtronic Inc. 8200 Coral Sea St., N.E. Mounds View, MN 55112, USA
Dr. Hae Lim (Medtronic member)	Medtronic Inc. 8200 Coral Sea St., N.E. Mounds View, MN 55112, USA
Dr. Ralf Meyer (Medtronic member)	Medtronic International Trading Sárl Route du Molliau 31, Case postale 84 CH-1131 Tolochenaz – Switzerland
Petra Kremer (Medtronic member)	Medtronic International Trading Sárl Route du Molliau 31, Case postale 84 CH-1131 Tolochenaz – Switzerland