Clinical Investigation Plan

Clinical Investigation Plan	Spanish Registry of Cryoballoon Ablation
Clinical Investigation Plan Identifier	RECABA
Study Product Name	Arctic Front Advance® cryoballoon connected to a nitrous oxide conveying system and inserted through a steerable sheath (FlexCath Advance®) from Medtronic. The device is CE marked and will be used according to the IFU for the pulmonary vein cryoablation. In accordance with standard clinical practice, any devices available on the market at that time with the CE mark and having the indication of pulmonary vein cryoablation may also be used.
Local Sponsor	Medtronic Ibérica S.A.
Version	1.0
[redacted]	

1. Version History

Version	Summary of Changes	Details of Author
1.0	• Not applicable, new document	[redacted]

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2. Glossary

Term	Definition
AEMPS	Spanish Agency of Medicines and Medical Devices
AE	Adverse Event
SAE	Serious Adverse Event
EC	Ethics Committee
CRF	Case Report Form
AF	Atrial Fibrillation
CIP	Clinical Investigation Plan

3. Synopsis

TITLE	Prospective observational study of pulmonary vein cryoablation in subjects with Atrial Fibrillation (AF) in Spain.
Type of Study	Post-market non-interventional study
Study Product Name	Arctic Front Advance® cryoballoon connected to a nitrous oxide conveying system and inserted through a steerable sheath (FlexCath Advance®) from Medtronic. The device is CE marked and will be used according to the IFU for the pulmonary vein cryoablation. In accordance with standard clinical practice, any devices available on the market at that time with the CE mark and having the indication of pulmonary vein cryoablation may also be used.
Sponsor	Medtronic Ibérica S.A., Avenida María de Portugal, 11, 28050 Madrid (Spain)
Indication under investigation	Pulmonary vein cryoablation in subjects with AF
Investigation Purpose	To reflect on standard clinical practice in pulmonary vein cryoablation in Spanish hospitals, the different procedure protocols, details of intervention, complications, long-term follow-up strategy and results in these subjects.
Product Status	The medical device has the CE mark and will be used according to the authorized instructions for use
Primary Objective	Evaluate the efficacy of the cryoablation procedure at 12 months, defined as the absence of recurrences of atrial fibrillation
Secondary Objectives	• Description of the profile of subjects who undergo this type of procedure (demographic factors, cardiovascular risk factors, medication, physical activity, sleep apnea, alcohol, smoking, chronic pulmonary disease, obesity, etc.). • To evaluate the acute efficacy of the procedure: complete isolation of the pulmonary veins demonstrated by the successful electrical disconnection of the pulmonary veins in the cryoablation procedure. • Description of the complications related to the procedure. • To evaluate the use of healthcare resources which this cryoablation procedure entails. **ANCILLARY Objectives** The participating sites may send proposals for additional analyses over the course of the study as long as they do not interfere with the primary objectives.

Study Design	Observational, prospective, national multicenter study
Sample Size	The observational study plans to enroll around 1000 subjects in approximately 30 Spanish sites. The enrollment period will be 2 years plus a minimum of 1 year of follow-up, with the possibility to extend it.
Inclusion/Exclusion Criteria	**Inclusion Criteria** ▪ Signature of the Data Release Form ▪ Subjects ≥ 18 years old ▪ Subjects who meet the indication for the cryoballoon ablation procedure, in accordance with current guidelines for standard clinical practice. **Exclusion Criteria** ▪ Subjects with a life expectancy of less than 12 months. ▪ Subjects who meet the exclusion criteria defined by local legislation (e.g., age, pregnancy, breastfeeding, etc.). ▪ Subjects who may currently be enrolled, or who plan to take part, in a study with a drug or device that may cause bias during the course of this study. Co-participation in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager..
Study Procedures	Clinical data will be collected at the baseline procedure and at the annual follow-up. There are no associated additional tests and only the necessary data will be collected in accordance with the variables taken into account in the Case Report Form.
Safety Assessments	The products used have the CE mark and are used according to the authorized indications for use. However, it is the investigator's responsibility to comply with any requirements for the reporting of Adverse Events (AE) as required by the Clinical Investigation Plan, by local legislation, and the specific requirements of each EC. Product experiences will be reported in accordance with the monitoring system through the regular channel from the vigilance system.
Statistics	The quantitative variables are expressed as mean, median, typical deviation and interquartile range depending on which is most suitable for the distribution of values. The differences between groups in relation to the quantitative variables will be evaluated through the student *t* test for independent samples or the analysis of variance (depending on the number of groups compared) and between variables through the student t test for related samples or the analysis of variance of repeated measures, as applicable. The intermediate statistical reports proposed by the investigators will depend on the hypotheses suggested by the investigator.

	A nominal significance of α=0.05 will be assumed for a result to be considered statistically significant. The statistical analysis will be achieved using the statistical packet SPSS 20.0.

4. Introduction

4.1. Background

Atrial fibrillation (AF) is the most common clinical arrhythmia in the general population[1]. Its prevalence increases with age and other cardiovascular risk factors and its morbi-mortality is considerably high, which implies a significant cost to health[2]. Given the characteristics of the current population, AF is considered one of the most significant cardiovascular health problems that could become a pandemic in the 21st century[3].

Since 1998, when Haïssaguerre et al[4] described how ectopic heartbeats originating in the pulmonary veins were the main trigger of atrial fibrillation (AF), treatment with curative expectations of these subjects focused on electrical isolation of the pulmonary veins. For this, different procedures and sources of energy were designed, of which point-by-point radiofrequency has been the most extensive technique up until now. However, pulmonary vein ablation with radiofrequency is a very laborious technique and not without complications. With the intention of facilitating the procedure, different techniques have been developed that try to isolate the pulmonary veins with a single application ("single-shot" devices)[5]. Of these devices, pulmonary vein cryoballoon ablation is the technique that has gradually been established in recent years as a more extensive alternative to radiofrequency ablation and with excellent long-term results in different published series in subjects with paroxysmal AF[6-15]. In these subjects, cryoablation seems to be at least as effective and safe as radiofrequency ablation, requiring less training time and a shorter time for the procedure and exposure to radioscopy[10,16-20].

However, despite being a successful emerging technique, there are not many multicenter studies and Registries. Of those, the German cryoablation registry[21] and the Freeze registry and its sub-studies[22] stand out, in which several European sites took part (mainly German sites). In Italy, sets of subjects with paroxysmal and persistent AF have been reported sporadically, however there is no multicenter registry that describes the characteristics of the subjects who have undergone to AF cryoablation and the long-term results of these subjects.

4.2. Device information

The Arctic Front Advance® connected to a nitrous oxide conveying system is used for pulmonary vein cryoablation which is inserted through a steerable sheath (FlexCath Advance®). The system progresses to the pulmonary vein ostium through a single transseptal catheterization and the balloon impacts against the venous ostium. When the nitrous oxide circulating through the system in a liquid state is released into the inside of the balloon through 8 ejectors, it leads to the switch from a very high pressure system to a very low pressure system. The sudden decompression of nitrous oxide in a liquid state means that it is transformed into a gas, causing a powerful endothermic reaction that absorbs heat from the adjacent tissues (*Joule-Thompson effect*)[23]. This reaction is the basis of the lesion caused by cryotherapy. Aerated and reheated nitrous oxide returns to the console through a connected vacuum system. For the registration of pulmonary vein potentials in real time, a circular octapolar electrode catheter (Achieve™) is used during the ablation with an interelectrode distance of 4-6 mm (depending on the diameter of the catheter) which is inserted through the lumen of the balloon. The special configuration of the Achieve™ catheter with a rigid proximal consistency 0.9 mm diameter high supporting guidewire, can be used as a supporting guidewire for the balloon on the one hand and as a mapping and stimulation electrode on the other[24-27].

Currently at least 2 applications of cryothermia through the pulmonary vein with a duration of 180 seconds are recommended. However, you need to keep in mind that the dosing recommendations are based on data from former investigational studies of focal cryoablation[28,29]. It is obvious that none of the tissue properties, the technology, or the coolants that were used are the same as those used nowadays for pulmonary vein cryoablation. This has meant that, despite the recommended application parameters, new protocols have been trialled with shorter application times and a lower number of applications per vein. The reduction in the application times of cryothermia seems to also reduce some of the complications arising from the technique such as phrenic paralysis, a circumstance which occurs more frequently after the first minute of application and during extra application after the disconnection[30,31,32].

If, as in the cryoablation procedure, there are differences in the protocol between sites, there is also diversity in terms of the follow-up of these subjects. At some sites, monitoring systems are used that vary between ones of very low sensitivity (24-hour Holter monitor) and those that use high-sensitivity devices such as implantable event recording systems.

To carry out the observational study, the devices mentioned previously will be used as well as future models that obtain the CE mark and are available on the market throughout the study, and that can be used in accordance with standard clinical practice.

4.3. Purpose of the study

With this study we propose the performance of a prospective registry of pulmonary vein cryoablation in subjects with paroxysmal or persistent AF at Spanish sites.

5. Study objectives and endpoints

5.1. Objectives

5.1.1. Primary Objective

To evaluate the efficacy of the cryoablation procedure at 12 months, defined as the absence of recurrences of atrial fibrillation.

5.1.2. Secondary Objectives

- Description of the profile of subjects who undergo this type of procedure (demographic factors, cardiovascular risk factors, medication, physical activity, sleep apnea, alcohol, smoking, chronic pulmonary disease, obesity, etc.).
- To evaluate the acute efficacy of the procedure: complete isolation of the pulmonary veins demonstrated by the successful electrical disconnection of the pulmonary veins in the cryoablation procedure.
- Description of the complications related to the procedure.
- To evaluate the use of healthcare resources which this cryoablation procedure entails.

5.1.3. Ancillary Objectives

It is considered that the participating sites may send proposals for additional analyses during the course of the study as long as they do not interfere with the primary or secondary objectives.

5.2. Endpoints

5.2.1. Primary endpoint

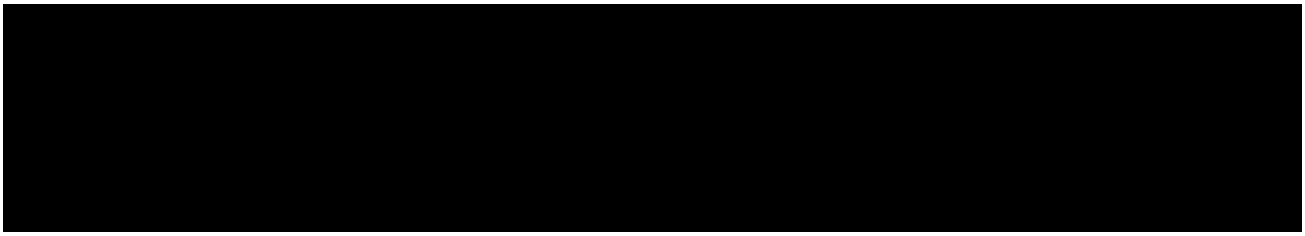
The primary and secondary endpoints coincide with the primary and secondary objectives defined in section 6.1.

6. Study Design

It is an observational, prospective, national study of subjects who undergo pulmonary vein cryoablation. All subjects (as long as they meet the I/E criteria) who undergo pulmonary vein cryoablation for atrial fibrillation will be enrolled at Spanish sites with demonstrable experience of the technique (at least 10 procedures a year), anonymously and with a secure web form.

6.1. Duration

It will last approximately 3 years: 2 years of enrollment and 1 year of follow-up. The follow-up period may be increased if it is deemed necessary for the progress of the study by the Scientific Committee and the Sponsor.



7. Product Description

Arctic Front Advance® cryoballoon connected to a nitrous oxide conveying system and inserted through a steerable sheath (FlexCath Advance®) from Medtronic. The device is CE marked and will be used according to the IFU for the pulmonary vein cryoablation. In accordance with standard clinical practice, any devices available on the market at that time with the CE mark and having the indication of pulmonary vein cryoablation may also be used.

The devices will not be provided as part of the study by the Sponsor. Sites will use those commercially available at their sites.

8. Subject selection

8.1. Study population

The sample size will be approximately 1000 subjects who must be enrolled over the two-year period, based on the annual rate of cryoballoon ablations carried out in Spain.

All local and regional regulatory requirements must be met before the activation of each site and before the enrollment of subjects in the study. Each participating site should have the official confirmation from the sponsor authorizing them to start any study activity.

Enrollment will last for 2 years. It is expected to commence in May 2016 and finish in May 2018.

A subject will be considered to be enrolled in the observational study from the moment in which he/she signs the Data Release Form for the study.

The investigator will keep a register of all the subjects enrolled in the study, linking each subject to a specific identification code for that site and that subject. This code will be assigned automatically by the electronic Case Report Form and will not contain any of the subject's personal information, so that the anonymity of the participating subjects is assured.

8.2. Subject enrollment

Those subjects who meet ALL of the inclusion criteria and none of the exclusion criteria may be enrolled in the observational study.

Subjects will be considered as included in the study from the moment they sign the Data Release form providing consent to collect their data.

Patient files for those subject enrolled in the registry will need to be clearly identified as subject participating in clinical study.

8.3. Inclusion criteria

- Signature of the Data Release Form
- Subjects ≥ 18 years old
- Subjects who meet the indication for the Cryoballoon Ablation procedure.

8.4. Exclusion criteria

- Subjects with a life expectancy of less than 12 months.
- Subjects who meet the exclusion criteria defined by local legislation (e.g., age, pregnancy, breastfeeding, etc.).
- Subjects who may currently be enrolled, or who plan to take part, in a study with a drug or device that may cause bias during the course of this study. Co-participation in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager.

9. Study Procedures

It is an observational study whereby the participating sites will carry out the cryoablation procedure in accordance with standard practice at their site. During this baseline procedure and during follow-up, there are no related additional tests and only the data deemed necessary according to the Case Report Form will be collected.

9.1. Schedule of events and data collection

Clinical data will be collected at specific times throughout the observational study. The data will be collected through an electronic data collection system for clinical trials (eCRF).

The collection of data can only be carried out once the subject has signed the Data Release Form for the study. The requirements for the collection of data are shown in Table 1.

The variables collected from the subjects will be as follows:

Baseline procedure:

1.- Demographic factors, cardiovascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, smoking), physical activity, sleep apnea, body mass index.

2.- Evolution time of the arrhythmia, previous anti-arrhythmic treatments, previous cardioversions.

3.- Anatomical data arising from the imaging tests (left ventricular parameters, ejection fraction, ventricular wall thickness, diameter, area or volume of the left atrium, pulmonary vein drainage pattern, pulmonary vein diameters)

4.- Procedure variables: number of applications per vein, application time, registration of pulmonary vein potentials during the ablation, time to block the vein, minimum temperature reached, reheating time, isolation or not of the pulmonary vein, results of the adenosine test, procedure time, exposure time to radioscopy, complications, temperature details in each of the applications, temperature at the time of isolation.

Annual follow-up (+/- 28 days):

5.- Variables during follow-up: anti-arrhythmic treatment, clinical recurrence of arrhythmia, result of the continuous ECG monitoring, 12-lead ECG, Nuubo monitoring method, etc. according to the protocol for each site.

A blanking period of 3 months has been established.

TABLE 1: Data collection requirements

	Inclusion	Baseline visit	Procedure	Follow-up
IC signed and dated	x			
Subject demographics		x		
Medical history		x		
Cardiovascular medication		x		x
Echocardiography		x		
Pulmonary anatomy		x		
Procedure data			x	
AF monitoring test				x
Healthcare resource utilization			x	x
Adverse Events	**When it occurs**			
Study Exit	**When it occurs**			

9.2. Investigation Site Selection

An investigation site may be included in the observational study if the site meets the following requirements:

- The site has demonstrable experience of the technique (at least 10 procedures a year),
- The site has adequate resources, facilities, equipment and support staff
- The site is capable of complying with the requirements of the registry, laws and local regulations, as well as Medtronic's requirements

According to local requirements a Clinical Trial Agreement or Investigator agreement will be in place depending on site specifics.

In order to document investigator experience and qualification a current (within 2 years) CV from the investigators will be collected

9.3. Subject Informed Consent – data release form

The investigator or designee must inform the subject about everything related to the observational study, using words which can be understood by the subject.

The investigator must give the Data Release Form to the subject and it must be signed and dated, in duplicate, by the subject him/herself (or by a legal representative) and by the investigator of the observational study, before carrying out any type of activity related to the registry or before making use of the subject's personal information.

The subject must keep a copy duly signed and dated by both parties. The Investigator will keep the other copy in the archives for the observational study at the site, duly signed and dated.

The subject must be given the opportunity to check the details of the observational study and to have adequate time to decide whether he/she wants to take part in the observational study or not. The investigator must respond to all the questions that the subject may want to ask.

The details of the observational study can only be sent to the sponsor after the signature process of the Data Release Form.

Personal data will be processed at all times with due confidentiality and privacy, and in accordance with the applicable regulations on data protection and privacy, in particular in compliance with Spanish Organic Law 15/1999, of December 13, 1999, on personal data protection and with its secondary legislation, including Royal Decree 1720/2007, of December 21, 2007, Regulation implementing Organic Law 15/1999 and Law 41/2002, of November 12, 2002, on basic regulations for subject autonomy.

In accordance with current legislation, the subject may exercise his/her right to access, correct, delete and object to his/her personal data to the Principal Investigator, who will direct his/her request to the person responsible for the archiving of personal data at the hospital or to the sponsor. The request must specifically include the following: name, last name(s), copy of the requester’s identification document, the study in which he/she is participating, description of his/her request and an address recorded for carrying out the process.

9.4. Training requirements

Prior to the activation of the investigation site in the study, Medtronic will provide relevant and pertinent training about the study for the personnel involved in the conduct of study activities and the investigator's responsibilities.

Training will be provided on:

- Clinical Investigation Plan (CIP)

- Signature process of the Data Release Form.
- Database management
- Applicable local regulations

9.5. Study materials and study specific equipment

The following material will be provided to each site for the performance of the study:

- Investigator's File
- Access to the electronic Case Report Form (CRF)
- Hard copy of subject worksheets with study-specific data to be collected.

The sponsor will not provide any medical devices used in this registry since it is an observational study.

There is no study specific equipment as the equipment used per standard of care is the one to be used.

9.6. Safety assessment

The products used have the CE mark and are used under the authorized indications for use according to their label. However, it is the investigator's responsibility to comply with any requirements for the reporting of Adverse Events (AE) as required by the Clinical Investigation Plan, by local legislation, and the specific requirements of each EC.

The investigators of this registry will report any deficiencies/malfunction and any adverse events related to the medical device through the regular channel from the vigilance system. As part of Medtronic's continual post-marketing safety assessment, Medtronic will evaluate those experiences and events and will produce monitoring reports for the local competent authorities as required.

In this registry, the adverse events will be reported through the eCRF. The investigator must enter all the information on the eCRF as soon as possible and before 10 calendar days from awareness date of the event, as long as the regulatory authorities do not require stricter timelines.

9.7. Data collection

The investigator and the members of his/her team must ensure the accuracy, integrity and authenticity of the data entered on the CRF. The sites will have the option to collect study data using the site worksheets, although the use of these is optional.

The data will be collected through an electronic data collection system for clinical trials. To facilitate the task of data collection, the sites will have paper copies of the sites' worksheets that contain the required information in accordance with the Clinical Investigation Plan for optional use in case the data are not captured elsewhere in the patient file. These will be stored in the study files.

The data entered on the CRF will come from the source documents and will be consistent with them. The investigation site team will create and store the source documents (such as the subject's clinical records, the ECGs, the subject's medical records, laboratory results, etc.). Only the persons authorized by the principal investigator may complete the CRF and only the investigator or designee authorized by the Principal Investigator may sign the CRF..

The Electronic Data Capture system maintains an audit trail on entries, changes or corrections in CRFs. If an individual authorized to complete the CRF makes changes to a CRF that has already been signed, the investigator must go sign the CRF again.

9.8. Protocol deviation handling

Because it is an observational study where the site's standard clinical practice is to going to be studied, and the protocol is drafted on that basis, no deviations from the protocol are foreseen.

Investigator must not deviate from the CIP.

In case there is any specific PD related to CIP or Good Clinical Practice (such as subject not signing Data Release Form and subject data collected) a PD form will be completed in the CRF and corrective/preventive actions will be identified.

Protocol Deviations will need to be reported to local ECs per local requirements.

9.9. Subject withdrawal or discontinuation

The study investigators can decide to remove the subject from the study in the following situations:

- Loss to follow-up over the course of the study. A patient will be considered as lost to follow after 3 attempts have been done to contact the patient without success and those are appropriately documented in the source documents
- Does not meet inclusion/exclusion criteria.
- The investigator thinks that it would be advisable for the subject to leave the study.

On the other hand, the subject has the right to terminate his/her participation in the study at any time during the course of the study.

10. Risks and benefits

10.1. Potential risks

Because it is an observational study of marketed products, there are no additional risks through participating in the study.

In the study, the products will be used in accordance with their labeling, therefore no risks different from those normally associated with standard clinical practice of the device are foreseen.

10.2. Potential benefits

There are no direct benefits for the subject arising from participation in the study. However, the information obtained through this study may result in an improvement of the knowledge of the subject population with atrial fibrillation and of the procedure to follow in cryoballoon ablation of these subjects. On the other hand, the information extracted from the usual processes at the participating sites can significantly help to standardize the suitability of treatment depending on the different clinical profiles.

10.3. Risk-benefit rationale

Section not applicable since there are no additional risks from participating in the registry or direct benefits for the subject arising from his/her participation in it.

11. Adverse Events Assessment

11.1. Definitions/Classification

The products used have the CE mark and are used under the authorized indications for use according to their label. However, it is the investigator's responsibility to comply with any requirements for the reporting of Adverse Events (AE) as required by the Clinical Investigation Plan, by local legislation, and the specific requirements of each EC.

An adverse event (AE) is any unfavorable medical incidence, unexpected disease or lesion, or any unfavorable clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether this is related or not to the medical device, and whether this is envisaged or not in the instructions for use.

A USADE is defined as any SAE relating to health, safety or any potentially fatal problem or death, caused by a device or associated therewith, that has not been identified previously in nature, intensity or level of incidence in the investigation plan, in the instructions for use or in the leaflet.

The incorrect functioning of the device is defined as the non-compliance with the specifications for use of the device or its functioning in a different way to the one specified for the known indication.

11.2. Adverse Event and Device Defficiency reporting

The investigators of this registry will report any deficiencies/malfunction and any adverse events related to the medical device through the regular channel from the vigilance system. As part of Medtronic's continual post-marketing safety assessment, Medtronic will evaluate those experiences and events and will produce monitoring reports for the local competent authorities as required.

The investigator must notify the sponsor or its representative and the reviewing EC of any unexpected adverse event of the device, within 24 hours from awareness date.

In this registry, the adverse events will be reported through the eCRF. The investigator must enter all the information on the eCRF as soon as possible and before 10 calendar days from awareness date of the event, as long as the regulatory authorities do not require stricter timelines.

The following adverse events will be collected in this registry:

- Unanticipated Serious Adverse Device Events (USADE):
- All adverse events that lead to death.
- All adverse events related to the procedure (up to 30 days post-procedure), such as (non-exhaustive list):
    - Access site complications:
        - Arteriovenous fistula
        - Pseudoaneurysm
    - Endocarditis
    - Cardiac damage (including myocardial infarction)
    - Embolic complications (including stroke)
    - Tamponade (associated or not to urgent surgery)
    - Hemorrhage requiring transfusion
    - Temporal Paralysis of the phrenic nerve

- Persistent Paralysis of the phrenic nerve
- Pulmonary vein stenosis
- Intense cephalea
- Hemoptysis
- Gastroparesis
- Mitral valve tearing
- Temporary STU elevation

Note: Early recurrences of AF/AFL/AT after the cryoablation process are to be expected. If these recurrences, which may require hospitalization of the subject or extension of his/her hospitalization, are within the "blanking" period, they will not be considered greater complications than the cryoablation procedure.

Note 2: temporal paralysis of phrenic nerve is defined as decrease in diaphragmatic excursion resolved prior to end of procedure. Detection of phrenic nerve damage prior to detectable decrease in diaphragmatic excursion during procedure will not be considered as AEs.

- All adverse events related to AF not related to the procedure (that appear after 30 days, throughout the study), which could be (non-exhaustive list):
  - Cardiovascular death
  - Systemic embolism
  - Congestive heart failure
  - Hemorrhagic events without stroke
  - Myocardial infarction
  - Stroke
  - Arrhythmia: atrial flutter or inappropriate sinus tachycardia or sinus dysfunction after the blanking period
  - Recurrence of AF or left flutter after the blanking period

  Note: The cases of recurrence of AF and the hospitalizations arising from AF will be collected in the adverse event form even though they will be processed as part of the analysis of the efficacy and not safety variables.

The investigator has to specify on the eCRF whether an adverse event can be deemed to be serious or not. If the adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

- Led to death
- Caused serious deterioration in the subject's health that has:

  a) resulted in a life-threatening illness or injury, or

  b) resulted in a permanent impairment of a body structure or a body function, or

  c) required in-subject hospitalization or prolongation of existing hospitalization, or

  d) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

Note: Planned hospitalization for a pre-existing condition is not considered a serious adverse event.

Note 2: Hospitalization is defined as patient staying overnight at the hospital (more than 24h)

The investigator also has to evaluate on the eCRF whether there is a reasonable possibility that the device may have caused or contributed to an AE. The factors that could be considered are time relationships, biological plausibility, the association (or lack of association) with the underlying disease and the presence (or absence) of a more likely cause. If an adverse event is classiffied as potentially related to the device this should be also notififed following the regular communication channels of the vigilance system.

All the data collected relating to adverse events will be reviewed remotely to ensure the correct reporting and classification of the event. In the event of having doubts about the classification and relationship with the device established by the investigator, the Scientific Committee will be consulted.

12. Data Review Committees

There will be a Publications Committee. Applicable information regarding Publication policy is described in the Publication Plan, separate document from this Protocol.

13. Statistical design and methods

The following statistical analysis plan of the data will be carried out:

The variables analyzed will be those collected in the subject registry corresponding to the different protocols of the procedure, intervention data, complications, follow-up and long-term results in these subjects. In the Method section there is a list of variables of interest.

Recurrence of AF will be defined as a clinically diagnosed episode of AF and accordingly documented (on ECG, Holter monitor with a duration of at least 30 seconds or implantable devices or event recording systems).

It is expected to carry out 3 analyses of the primary and secondary objectives described in the Clinical Investigation Plan:

1. At the end of the first year of enrollment
2. At the end of the second year of enrollment
3. At the end of follow-up

On the other hand, there will be 4 analyses of additional proposals throughout the study (see Appendix B: Publications Plan)

- Two analyses at the end of enrollment.
- Two analyses at the end of follow-up.

Each of the variables of interest will be described univariantly and individually.

Crosses of variables will also be carried out to describe each one of the clinical strata of interest.

When it is possible and of interest for the investigators, statistical comparisons between strata will be carried out through statistical tests.

Specific statistical models to respond to the interests of the investigators will be proposed, such as comparison of the procedures or comparison of subject strata.

13.1. Analysis of clinical data

It is expected to include approximately 1000 subjects enrolled at approximately 30 Spanish sites, with an enrollment period of 2 years and a follow-up period of one year from the time of enrollment of each subject. The subjects analyzed will be the ones included in the RECABA study database: "Spanish Registry of Cryoballoon Ablation". The variables analyzed will be those mentioned previously with the intention of adequately describing the activity of the clinical sites, the procedures used and the diseases treated in accordance with standard clinical practice.

All the data are anonymized in origin so that it is not possible to identify the subjects.

The collection of data will be prospective from the time of enrollment.

The database will be received codified and debugged, and the allocation of the lost values that have been decided previously.

The basic report at the end of enrollment and at the end of the follow-up period will consist of: The quantitative variables are expressed as mean, median, typical deviation and interquartile range depending on which is most suitable for the distribution of values. The differences between groups in relation to the quantitative variables will be evaluated through the student *t* test for independent samples or the analysis of variance (depending on the number of groups compared) and between variables through the student t test for related samples or the analysis of variance of repeated measures, as applicable. To analyze the relationships between categorical variables the chi-squared test (χ^2) and the Fisher's exact test will be used. The differences of proportions will be assessed through the homogeneity test χ^2. To assess the relationships between the quantitative variables the Pearson or Spearman *r* correlation will be used, as appropriate.

The intermediate statistical reports proposed by the investigators will depend on the hypotheses suggested by the investigator. They will include at least a descriptive analysis such as the one described previously. In addition, the appropriate models to respond to the hypotheses proposed will be estimated, which can include techniques of the style of exploratory factor analysis, analysis of multiple contingency, analysis of logistical regression, analysis of conglomerates or analysis of multifactorial variance.

A nominal significance of α=0.05 will be assumed for a result to be considered statistically significant. The statistical analysis will be achieved using the statistical packet SPSS 20.0.

14. Ethics

14.1. Statement(s) of compliance

The study will be conducted in compliance with the most recent version of the Declaration of Helsinki, Spanish laws and regulations (Royal Decree 1090/2015, Royal Decree 1616/2009, Order SAS/3470/2009 of 16 December), including data protection laws mentioned in previous section, the clinical investigation contract and the Clinical Investigation Plan.

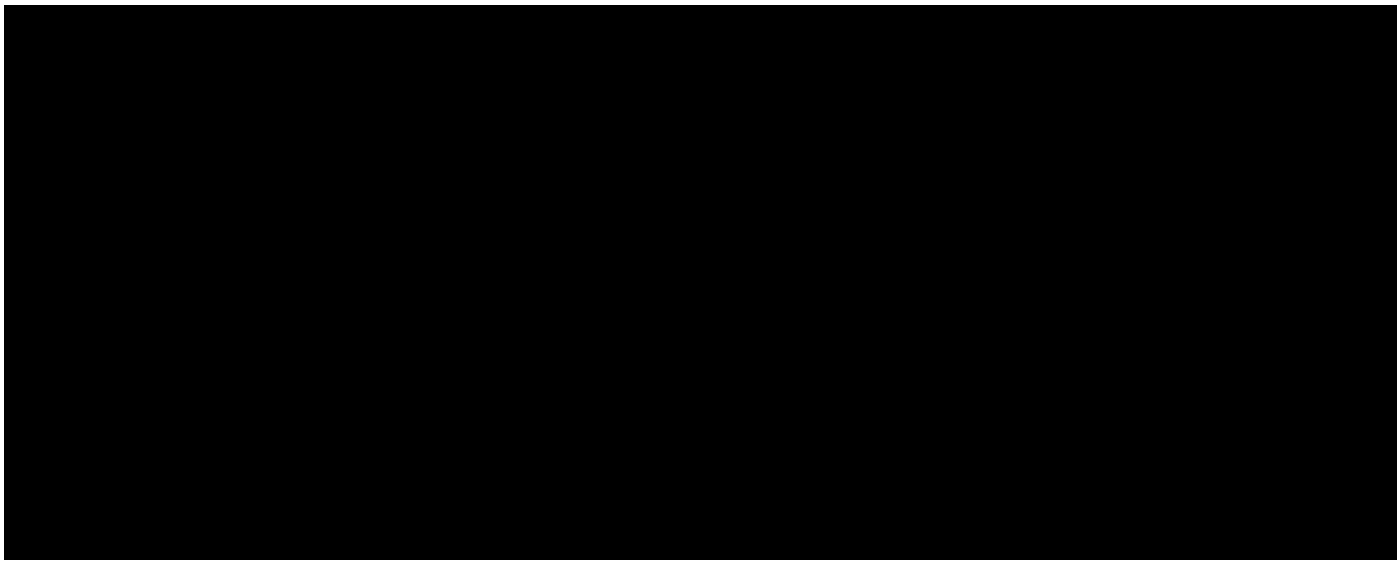
All the principles of the Declaration of Helsinki have been implemented in this observational study through the signature process of the Data Release Form, approval by the Clinical Research Ethics Committee, training in the study, registration of the observational study, publication policy, etc.

This observational study does not require the authorization of the Spanish Agency of Medicines and Medical Devices (AEMPS), as stipulated in Royal Decrees 1090/2015 and 1616/2009 since it is a clinical investigation with medical devices which already hold the CE mark and these are used in accordance with the clinical purpose taken into account in the pertinent procedure of evaluation of compliance.

Since it is an observational study where standard clinical practice is being followed with products with CE mark in accordance with local legislation, the evaluation and approval of the observational study by a single Ethics Committee (EC) of one of the participating sites is considered sufficient. Once the reference

EC approval has been obtained, the EC from each participating site will assess whether it is necessary to evaluate the local aspects of the observational study. Any additional requirements imposed by the EC shall be followed. If any action is taken by the EC with respect to the investigation, that information will be forwarded to the sponsor.

15. Study Administration



15.2. Data Management

The data from the CRF will be stored in a secure, password-protected database. The data will be reviewed through manual and scheduled data edit checks. The discrepancies will be raised at the sites to proceed to their resolution through queries. At the end of the study, the data will be stored as a frozen data set and Medtronic will store them.

15.3. Direct access to source data/documents

Medtronic may conduct audits at participating investigational sites. The purpose of an audit is to verify that the activities related to the study are performed properly. The regulating authority may also carry out inspections in the participating research sites. All announcements of inspections by the regulating authority must be reported as soon as possible to the Sponsor.

The investigator and/or the institution must allow the Sponsor and designated representatives by the Sponsor and the regulatory organizations direct access to the data and source documents, taking into consideration all of the restrictions of local laws, to carry out monitoring related to the study, audits, and regulatory inspections.

15.4. Confidentiality

Personal data will be processed at all times with due confidentiality and privacy, and in accordance with the applicable regulations on data protection and privacy, in particular in compliance with Spanish Organic Law 15/1999, of December 13, 1999, on personal data protection and with its secondary legislation, including Royal Decree 1720/2007, of December 21, 2007, Regulation implementing Organic Law 15/1999 and Law 41/2002, of November 12, 2002, on basic regulations for subject autonomy.

15.5. CIP amendments

Medtronic will send all significant amendments to the Clinical Investigation Plan, including justification for these amendments, to the investigators and to the corresponding ECs for approval.

Amendments to the Clinical Investigation Plan must be agreed between the Sponsor and the Scientific Committee.

15.6. Record Retention

15.6.1. Study records

The records are subject to inspection by the health authorities. The records must be kept for at least 5 years after the date on which the study ends early or finally, and in accordance with local requirements.
The investigator will keep the following exact, complete, and up-to-date records related to the investigator's participation in this study:

- All correspondence with the EC, Medtronic, monitors, and competent authorities, including the reports required related to this study
- Records of the subjects' clinical history
- Signed Subject Data Release Form documents
- All relevant complaints from subjects
- Observations regarding adverse episodes
- Clinical Investigation Plan and amendments
- All the CRFs and sets of data required by the Clinical Investigation Plan
- Signed clinical trial agreements
- Authorizations, renewals, and correspondence from the EC

15.6.2. Sponsor records

Medtronic will keep, among others, the following records:

- All correspondence (including the correspondence with the authorities and the EC, if necessary) relating to the investigation, including the EC authorization letter
- Signed clinical trial agreement
- All serious adverse events
- All of the site's specific forms for subject informed consents
- Clinical Investigation Plan and amendments
- Name of the main investigators and the sites where the clinical research will be performed
- Approval of the study documents
- Electronic CRF

15.7. Publication and use of the information

The Publication Plan, separate document from this Protocol, describes the procedures for the development of publications, criteria for determining authorship, prioritization of proposals, and

procedures for developing, revising, and approving abstracts, manuscripts, and public presentations. The Publication Plan internally approved by the Scientific Committee and Medtronic will be used as a guide for publications process.

The transparency of the study results will be maintained in the following manner: By registering the study on ClinTrials.gov, recording and communicating the results on ClinicalTrials.gov; by presenting the publication of the results of the objectives defined in the protocol after its conclusion and the results of the complementary proposals throughout the study; by divulging the financial interests of the authors of the publication according to the policies established by the corresponding journals and conferences; and by making the study data of each site accessible to the corresponding investigator after the trial has ended.

[redacted]

15.8. Early termination or suspension

15.8.1. Early termination or study suspension

The Sponsor or the regulating authority may decide to suspend or terminate the study prematurely (for example if information comes to light indicating that the risk for subjects participating in the study is greater than was indicated initially, or if the intermediate analysis indicates that the results differ significantly from the objectives or statistical evaluation criteria of the study).If the study is terminated prematurely or suspended, the Sponsor will inform the clinical investigators of the termination or suspension of the study and the reasons for this decision. The evaluating ECs and the subjects in the study or their legal representatives must be informed.

15.8.2. Early termination or suspension of the research site

The Sponsor, the EC of the site, or the regulating authority may decide to suspend or prematurely terminate a research site (due to, for example, cases of breach of the Clinical Investigation Plan or insufficient subject enrollment). If the investigational site is terminated prematurely or suspended, the Sponsor will inform the clinical investigators of the termination or suspension of the study and the reasons for this decision. If the site was evaluated by its own EC, the study closeout at the site must be reported, as well as the reference EC that evaluated it initially, and the study subjects at that research site or their legal representatives.

15.9. Study closeout

The study closeout will be reported with justification to the participating investigators, to the ECs that have evaluated the study, and to the Scientific Committee of the study.

It is the investigator responsibility to submit the final report to EC according to local requirements.

16. References

1.- Feinberg WM et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995; 155: 469-73.

2.- Go AS et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-5.

3.- Rienstra M et al. Novel risk factors for atrial fibrillation: useful for risk prediction and clinical decision making? Circulation 2012; 125: e941-6.

4.- Haïssaguerre et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. N Engl J Med 1998; 339: 659.

5.- Schmidt B et al. Balloon catheters for pulmonary vein isolation. Herz 2008; 33(8): 580-4.

6.- Ferrero A et al. Medium-term results of cryoballoon ablation of the pulmonary veins in patients with paroxysmal and persistent atrial fibrillation. First experience of a Spanish center. J Interv Cardiovasc Electrophysiol 2013; 37(2): 189-196.

7.- Neumann TH et al. Circumferential pulmonary vein isolation with the cryoballoon technique: results from a prospective 3-center study. J. Am. Coll. Cardiol 2008; 52; 273-278.

8.- Aytemir K et al. Immediate and medium-term outcomes of cryoballoon-based pulmonary vein isolation in patients with paroxysmal and persistent atrial fibrillation: single-centre experience. J Interv Card Electrophysiol 2013; 38:187-195.

9.- Chierchia GB et al. Second-generation cryoballoon ablation for paroxysmal atrial fibrillation: 1-year follow-up. Europace 2014; 16: 639–644.

10.- Schmidt M et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German ablation registry. J Cardiovasc Electrophysiol 2014; 25: 1-7.

11.- Vogt J et al. Long-term outcomes after cryoballoon pulmonary vein isolation results from a prospective study in 605 patients. J Am Coll Cardiol. 2013; 61(16): 1707-1712.

12.- Metzner A et al. One-year clinical outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon. Circ Arrhythm Electrophysiol 2014; 7:288-292.

13.- Fürnkranz A et al. Improved Procedural Efficacy of Pulmonary Vein Isolation Using the Novel Second-Generation Cryoballoon. J Cardiovasc Electrophysiol 2013; 24: 492-497.

14.- Di Giovanni G et al. One-Year Follow-Up After Single Procedure Cryoballoon Ablation: A Comparison Between the First and Second Generation Balloon. J Cardiovasc Electrophysiol 2014; 25: 834-839.

15.- Fürnkranz A et al. Improved 1-Year Clinical Success Rate of Pulmonary Vein Isolation with the Second-Generation Cryoballoon in Patients with Paroxysmal Atrial Fibrillation. J Cardiovasc Electrophysiol 2014; 25: 840-844.

16.- Kojodjojo P et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart 2010; 96: 1379-1384.

17.- Martí-Almor J et al. Resultados a largo plazo de la crioablación con balón para el tratamiento de la fibrilación auricular en un centro de bajo volumen. Rev Esp Cardiol 2014; 67(7):577–584.

18.- Mugnai G et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. Am J Cardiol 2014; 113: 1509-1513.

19.- Sorgente A et al. Atrial fibrillation ablation: A single center comparison between remote magnetic navigation, cryoballoon and conventional manual pulmonary vein isolation. Indian Pac Electrophysiol 2010; 10: 486-495.

20.- Wasserlauf J et al. Cryoballoon versus Radiofrequency Catheter Ablation for Paroxysmal Atrial. Pacing Clin Electrophysiol. 2015 Jan 28. doi: 10.1111/pace.12582. [Epub ahead of print].

21.- Schmidt M, Dorwarth U, Andresen S et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. J Cardiovasc Electrophysiol, 25 (2014), pp. 1–7.

22.- Straube F, Dorwarth U, Vogt J et al. Differences of two cryoballoon generations: insights from the prospective multicenter multinational FREEZE cohort substudy. Europace 2014; 16: 1434-1442.

23.- Andrade JG et al. The Biophysics and Biomechanics of Cryoballon Ablation. PACE 2012; 35:1162-1168.

24.- Chierchia GB et al. Pulmonary vein isolation during cryoballoon ablation using the novel Achieve inner lumen mapping catheter: a feasibility study. Europace 2012; 14: 962–967.

25.- Chierchia GB et al. Verification of pulmonary vein isolation during single transseptal cryoballoon ablation: a comparison between the classical circular mapping catheter and the inner lumen mapping catheter. Europace. 2012; 14(12):1708-14

26.- Chun J et al. Single transseptal big cryoballoon pulmonary vein isolation using an Inner lumen mapping catheter. PACE 2012; 20: 1-8.

27.- Dorwarth U et al. Pulmonary vein electrophysiology during cryoballoon ablation as a predictor for procedural success. J Interv Card Electrophysiol 2011; 32:205–211.

28.- Dubuc M et al. Transvenous catheter ice mapping and cryoablation of the atrioventricular node in dogs. PACE 1999; 22 :1488-1498.

29.- Dubuc M et al. Feasibility of cardiac cryoablation using a transvenous steerable electrode catheter. J Interv Cardiac Electrophysiol 1998;2:285–292.

30.- Andrade JG et al. Pulmonary vein isolation using a second-generation cryoballoon catheter: A randomized comparison of ablation duration and method of deflation. J Cardiovasc Electrophysiol 2013; 24: 692-698.

31.- Chierchia GB et al. Initial experience of three-minute freeze cycles using the second-generation cryoballoon ablation: acute and short-term procedural outcomes. J Interv Card Electrophysiol 2014; 39:145–151.

32.- Ciconte G et al. Single three-minutes freeze for second-generation cryoballoon ablation: one-year follow-up following pulmonary vein isolation. Heart Rhythm 2015;12:673-80.

17. Appendices

Appendix C: List of sites and participating investigators
An up to date investigator list will be kept separate and maintain regularly.

APPENDIX C

Potential list of research sites and participating investigators

An up to date investigator list will be kept separate and maintain regularly.

All sites in Spain with sufficient experience in cryoablation procedures (more than 10 procedures per year) will be invited to participate in the register. The potential list of sites that meet these characteristics is as follows:

#	**SITE**	CITY
1	H. Virgen de la Victoria	Málaga
2	H.NISA- Aljarafe Sevilla	Seville
3	H. U. Juan Ramón Jimenez	Huelva
4	H. Virgen Macarena	Seville
5	H. U. Reina Sofía	Cordoba
6	H. U. Virgen de la Nieves	Grenada
7	H. Clínico universitario de Valencia	Valencia
8	H. de Basurto	Bilbao
9	H. del Mar	Barcelona
10	H. U. Virgen de la Arrixaca	Murcia
11	H. U. Nuestra Sra. de la Candelaria	Santa Cruz de Tenerife
12	H.U. de Canarias	San Cristobal de la Laguna (Santa Cruz de Tenerife)
13	H. U. Gran Canaria Dr. Negrin	Las Palmas de Gran Canaria
14	H. U. Germans Trias i Pujol	Badalona (Barcelona)
15	H. Bellvitge	L'Hospitalet de Llobregat (Barcelona)
16	H. Quirón de Valencia	Valencia
17	H. U. Ramón y Cajal	Madrid
18	H. de la Santa Creu i Sant Pau	Barcelona
19	Clinical IMQ Zorrotzaurre	Bilbao
20	H. U. Puerta del Hierro	Madrid
21	H. U. San Juan de Alicante	Alicante
22	H.U. La Paz	Madrid
23	H. Montepríncipe	Boadilla del Monte (Madrid)
24	Centro Médico Teknon S.L.	Barcelona
25	H.G.U. Alicante	Alicante
26	H.Nuestra Señora de Fátima Pontevedra	Pontevedra

27	H. U. 12 Octubre	Madrid
28	H.U. Marqués de Valdecilla	Santander
29	H.U. Son Espases	Palma de Mallorca
30	H. U. Clínico San Carlos	Madrid
31	H. U. Clínic i Provincial de Barcelona	Barcelona
32	H.Miguel Servet	Zaragoza
33	H. Do Meixoeiro - CHUVI	Vigo (Pontevedra)
34	H.U. Donostia	San Sebastián
35	H. de Santiago	Santiago de Compostela
36	Complejo Hospitalario de Toledo	Toledo