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GOLD AF
Clinical Investigational Plan

GOLD AF
REGISTRY

Sponsor

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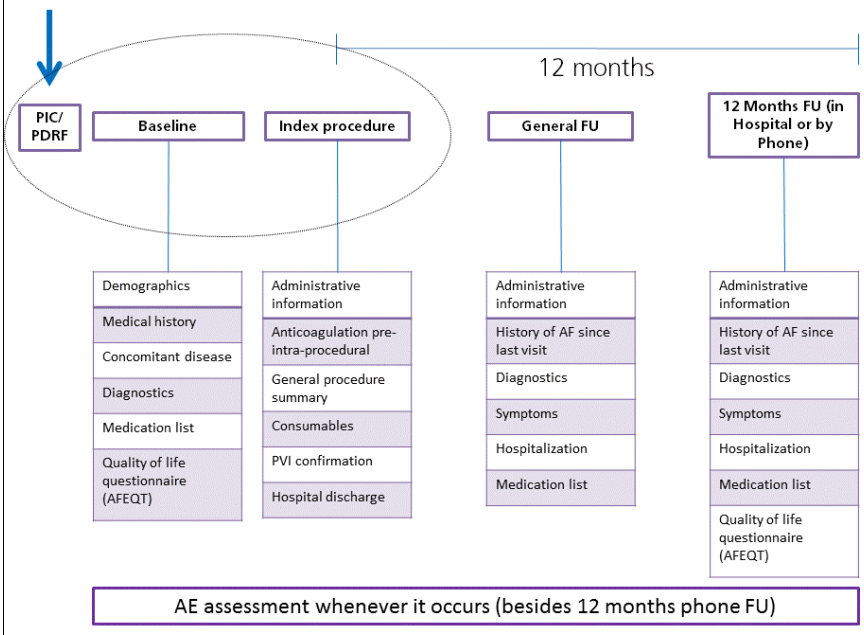
Glossary

AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
Afl	Atrial Flutter
AT	Atrial tachycardia
CFAE	Complex Fractionated Atrial Electrograms
CI	Confidence Interval
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Cardiac Resynchronization Therapy
CV	Cardio Version
EC	Ethical Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EP	Electrophysiology
FU	Follow up
ICD	Implantable Cardioverter Defibrillator
ID	Identification
IFU	Instructions for Use
IHF	Institut für Herzinfarktforschung
ILR	Implantable Loop Recorder
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
LA	Left Atrium
LMWH	Low-Molecular-Weight Heparin
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MAAC	Multi-Array Ablation Catheter
MASC	Multi-Array Septal Catheter
MI	Myocardial Infarction
MRI	Magnet Resonance Imaging
NA	Not Available
NIS	Non Interventional Study
NOAC	Novel Oral Anticoagulant
PAF	Paroxysmal AF
PAF	Paroxysmal Atrial Fibrillation
PDRF	Patient Data Release Form
PI	Principal Investigator
PIC	Patient Informed Consent Form
PMR	Post Market Research
PV	Pulmonary Vein
PVAC	Pulmonary Vein Ablation Catheter
PVI	Pulmonary Vein Isolation
QoL	Quality of Life
RF	Radiofrequency
RFA	Radiofrequency Ablation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

Synopsis

Title	GOLD AF Registry
Study design	Postmarket release (PMR), multi-national, multi-center, prospective observational study
Study descriptors	Prospective, registry, atrial fibrillation (AF), pulmonary vein isolation, Phased radiofrequency ablation (RFA)
Purpose	Describe the use of Phased RFA system in the "real world" clinical practice and to evaluate its performance.
System Description	The Phased RFA system is designed to be used for the creation of endocardial lesions (focal and linear) during cardiac ablation procedures for the treatment of symptomatic AF. The Phased RFA system is intended to deliver temperature-controlled radiofrequency (RF) energy from the GENius Multi-Channel RF Ablation Generator to user-selectable electrodes on compatible Phased RFA catheters. This over-the-wire multielectrode catheter delivers duty-cycled bipolar and unipolar RF energy at relatively low power. The power is limited to a maximum of 8–10 W per electrode, depending on the chosen bipolar/unipolar energy ratio. Additionally, the Phased RFA system performs as a pass-through for cardiac electrophysiological mapping and delivery of diagnostic pacing stimuli to/from external equipment.
Patient selection criteria	• Patient with AF who is scheduled for Phased RFA procedure • Patient signed patient informed consent or patient data release form • Age ≥18 years old To avoid enrollment bias in this cohort of patient and reflect "real world" clinical practice for Phased RFA no exclusion criteria will be defined.
Objectives	**Main objective:** • Estimate Phased RFA 12 months success rate **Ancillary objectives:** • Estimate Phased RFA safety • Characterize the acute procedural success rate • Assess Phased RFA efficiency • Characterize the peri-procedural anticoagulation therapy • Describe single catheter PVAC GOLD utilization in persistent AF • Evaluate QoL ("AFEQT" questionnaire)
Data Collection	Site Questionnaire (one time before the center enrollments and updates if new operators join the registry) • Rate of Phased RFA procedures during last three years • Average rate of PVIs during the year • Operator's ID • Experience of study delegated operators with Phased RFA Baseline • Enrollment • Demographics • Medical history a. History of cardiovascular disease (CVD) b. History of AF c. Symptoms • Concomitant diseases

	• Diagnostics (prior to procedure) • Medication list • Quality of life: AFEQT questionnaire Procedure • Administrative information • Anticoagulation pre-intra-procedural • General procedure summary • Consumables • PVI confirmation • Hospital discharge General FU • Administrative information • History of AF since last visit • Diagnostics • Symptoms • Hospitalization • Medication list 12 Months FU ("in hospital" if available by standard of care) • Administrative information • History of AF since last visit • Diagnostics • Symptoms • Hospitalization • Medication list • Quality of life: AFEQT questionnaire 12 Months FU by Phone (if "in hospital" visit is not a standard of care) • Administrative information • History of AF since last visit • Diagnostics • Symptoms • Hospitalization • Medication list • Quality of life: AFEQT questionnaire Adverse Event (AE): • AE Administrative information • AE Relatedness • AE Description • AE Management • AE Update Deviation Form: • Administrative information • Deviation description • Reason for deviation • Action taken • Comments (Optional) Study Exit form: • Date of exit • Reason of exit
Sites	Approximately 38 centers across Europe, Israel and South Korea. Additional sites and regions might be considered and added subsequently.
Patients	Approximately 1000 patients

Flow Chart	
Visits	All follow up (FU) visits in the registry are unscheduled. They will be performed in accordance with "routine clinical practice" in participating medical centers and reported in "General FU" case report form (CRF). If a patient is invited for FU to the medical center in the period of 12-14 months after the study ablation procedure, it should be documented in "12 months FU" CRF, which contains QoL questionnaire "AFEQT" above "General FU" information. If "12 month FU" is completed in the database, no further FU visits are required, and patient exits the study. As the "in hospital" 12 months FU is not a standard of care in some medical centers, 12 month phone FU may be conducted as an alternative. If 12 (+1) months after the procedure "12 months FU" CRF is not completed in the database, site personal will be notified to conduct the 12 month FU by phone and CRF "12 months FU by phone" is to be completed In Germany a delegated institution (IHF)) might conduct phone interview for 12 months FU at investigator's discretion, and based on what defined in the Clinical Study Agreement (CTA).
Individual FU duration	Maximum 14 months for each patient The follow up period starts from the date of the first Phased RFA procedure (hereafter „index") and lasts 12 (+ 2) months. In case the index procedure is unsuccessful (e.g. not all PVIs reached/isolated, procedure prematurely terminated due to patient's clinical status or technical issues), patients will continue their participation in the registry until the end of defined FU period.
Time schedule (tentative) for calendar years	Preparation Q2-Q4 2014 Recruitment Q1 2015 – Q2 2018 Intended last patient out Q3 2019 Final Report Q1 2020

1 Introduction

AF is the most common of the sustained arrhythmias affecting millions of people worldwide, with an estimated 2.2 million people in the United States (US) and 4.5 million in the European Union (EU) afflicted with the disorder (1). The overall prevalence of AF is between 2.3% and 2.8% (2). However, the prevalence increases with advancing age, with approximately 10% prevalence of AF in persons aged 70 years or older. The causes of AF are numerous and varied, including ischemic heart disease, post-cardiac surgery, sick sinus syndrome, hypertensive heart disease, idiopathic causes, etc. (3). The prognosis is related to the underlying cause of the disease, with idiopathic causes having the best prognosis and ischemic cardiomyopathy having a poor prognosis (4). AF is associated with an increased incidence of thromboembolic events (stroke and transient ischemia attack), heart failure, and all-cause mortality (5). It is a debilitating disease with symptoms that reduce quality of life and increase the number of hospitalizations. The management of AF is a challenge due to a heterogeneous etiology and tendency for self-propagation of AF, "AF begets AF".

Current AF treatment strategies include antiarrhythmic drug therapy, catheter based ablation, oral anticoagulation therapy to mitigate thromboembolic events, and therapy for concomitant diseases. However, antiarrhythmic drug therapy is often unsuccessful due to intolerance and/or ineffective treatment of AF and can increase the incidence of arrhythmia. Catheter ablation has shown to be a safe and effective treatment strategy for AF and therefore it has become an established invasive strategy for drug refractory AF. Approximately 50,000 ablations are performed annually in the US, and about 60,000 in Europe (6), and favorable outcomes suggest that this approach will remain a popular alternative to chronic drug therapy. Catheter ablation treatment strategies for AF have evolved over time and currently include isolation of the pulmonary veins (PVI) as the cornerstone of therapy. For patients with paroxysmal AF (PAF) PVI has been shown to be an effective treatment (7).

PVI has also been shown to be effective in patients with persistent and long-standing persistent AF (8).

However, for some patients with persistent/longstanding persistent AF, antral PVI alone may be insufficient as the location of drivers expands beyond the PVs into other areas of the left atrium and septum. In addition to PVI, linear and focal ablation strategies have demonstrated improved long-term outcomes (9). However, recent results from the STAR AF study have suggested, that additional linear or focal lesions may not improve efficacy compared to PVI alone (10). Overall, there is no consensus on the optimal ablation substrate for patients with persistent AF (11) and therefore different ablation strategies are utilized in various electrophysiology (EP) laboratories worldwide (12).

Historically, conventional point-by-point RF (hereto referred to as conventional) ablation procedures have often required advanced mapping and navigation tools (3-dimensional electro-anatomical mapping), tend to be long (4-6 hours) and need large numbers of ablations to achieve the desired therapeutic endpoint.

Recognizing the need for catheter improvement to shorten procedural times and potentially increase efficacy via contiguous lesions led to the development of the Medtronic Phased RFA system (Ablation Frontiers, Medtronic, U.S.) (13, 14).

PVAC GOLD and PVAC were designed to adopt an optimal anatomical geometric shape for the electrical isolation of the PVs. MASC was designed for ablations along the atrial septal wall. MAAC was designed to ablate arrhythmogenic drivers in the left atrial body, such as complex fractionated atrial electrograms (CFAEs). Previous studies have demonstrated that the predicate platinum electrode catheter, PVAC, effectively isolates PVs with an average acute procedural success of 98% and an average chronic efficacy of 74% with average follow up of 10 months (range from 3-24 months). The new PVAC catheter, PVAC GOLD, includes key design changes to improve RF energy delivery and mitigate emboli. To enhance RF energy delivery, the electrodes were changed to gold, which has ~4X the thermal conductivity of platinum, and a forward tilt of the array was included to increase contact force uniformity across the electrode array. In addition, the distal PVAC electrode was eliminated to avoid proximity of energized electrodes and avoid emboli formation. However, data on the implementation of PVAC GOLD has been less studied as it received CE mark on 21 November 2012.

The purpose of this prospective, observational study is to provide insight into daily routine of EP laboratories utilization of Phased RFA system in large number of patients in various countries by describing the clinical features of the patients treated, the approaches undertaken, the catheters used and further procedural details.

The registry will highlight the distribution of indications for PVAC GOLD ablation between paroxysmal and persistent AF, lone AF and AF with underlying disease. This registry will provide data on acute and mid-term success rates for Phased RFA. Additionally, this study will provide further information in the evolving

anticoagulation strategies (e.g. continuous versus bridging and vitamin K antagonist versus novel oral anticoagulants) in the setting of AF ablations (15,16).

2 Goal and Objectives

Study goal: Describe the use of Phased RFA system in the "real world" clinical practice and to evaluate its performance.

The study is intended to describe the following objectives.

Main objective:

- Estimate Phased RFA 12 months success rate

Ancillary objectives:

- Estimate Phased RFA safety
- Characterize the acute procedural success rate
- Assess Phased RFA efficiency
- Characterize the peri-procedural anticoagulation therapy
- Describe single catheter PVAC GOLD utilization in persistent AF
- Evaluate QoL ("AFEQT" questionnaire)

3 Study Methods

3.1 Summary of Study Design

The GOLD AF registry is a postmarket release (PMR), prospective, observational, multicenter, clinical study (hereafter "registry" can be used) in patients with AF treated with the Phased RFA system (Medtronic, Minneapolis, MN, USA). Patient's participation in this study has no impact on his or her indication, diagnostics or therapy. Subjects are supposed to be treated in compliance with current Instructions for Use (IFU) as well as according to medical society guidelines and the clinic's internal directives.

3.2 Study Population/Selection Criteria

Patients with paroxysmal, persistent and long-standing persistent AF who fulfill inclusion criteria.

Inclusion criteria:

- Patient with AF who is scheduled for Phased RFA procedure
- Patient signed Patient Informed Consent (PIC) or Patient Data Release Form (PDRF)
- Age ≥18 years old

Minimization of Bias

Selection of sites, selection of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- No exclusion criteria will be defined to reflect "real world" clinical practice approach to the Phased RFA therapy.
- Data collection requirements and study procedures will be standardized across all study centers.
- All study clinicians, participating site personnel, Medtronic and IHF (heater "CRO" can be used) personnel will be trained on the respective aspects of the study using standardized training materials.

3.3 Study Therapies

The Medtronic Phased RFA system is intended to be used for mapping intracardiac electrograms and delivering precise, temperature controlled radio frequency (RF) ablation therapy within the atria of the heart for the treatment of AF. The main components of Medtronic Phased RFA system are listed in Table 3-1.

Table 3-1: Medtronic Phased RFA system component information.

Model Number	Component	Market release
990018	GENius Multi-Channel RF Ablation Generator	Market released
990004	Catheter Interface Cable	Market released
990001	Multi-Array Septal Catheter (MASC)	Market released
990000	Multi-Array Ablation Catheter (MAAC)	Market released
990030	Pulmonary Vein Ablation Catheter (PVAC)	Market released/ Phased out
990078	Pulmonary Vein Ablation Catheter (PVAC GOLD)	Market released
990022	Tip-Versatile Ablation Catheter (T-VAC)	Market released
990028	ECG Interface Box	Market released
990020	ECG Interface Box Cable	Market released
990027	ECG Amplifier Cable	Market released
990029	GENius Jr. Remote Control	Market released
990041, 990042	Remote Control Cable 15 or 25ft	Market released

The System provides the ability to select or de-select various combinations of electrode pairs on the ablation catheters in order to provide tailored treatment for each patient based upon the individual's therapeutic needs. The system includes automatic closed loop temperature control to regulate ablation temperatures for all selected electrodes. Target temperatures are adjustable prior to and during ablation. The energy is duty cycle controlled to enhance lesion creation and improve safety during ablation. The catheter electrodes include proprietary design features that maximize heat transfer away from the target tissue. These features provide a means for creating effective lesions with a minimum amount of RF energy. The combination of optimal electrode design and the use of duty cycle controlled bipolar and/or unipolar currents, increases the safety profile of the system and delivers only the necessary amount of RF energy to create adequate lesions.
The System supports delivery of RF energy to all catheters listed in Table 3-1 above. The System has the ability to detect which catheter is connected and set appropriate system parameters. Energy delivery can be directed to desired locations within the heart utilizing bi-polar, uni-polar or 4:1, 2:1 and 1:1 bi-polar/uni-polar energy delivery options. These different energy settings allow the operator to titrate lesion depth and fill depending upon anatomy and other clinical considerations. Ablation duration is adjustable from 45 to 120 seconds in 5 seconds increments. The system includes a safety STOP switch to immediately terminate ablation energy if required during the clinical procedure. Included with the system is an ECG Interface Box, which provides a means for interrogation of patient intracardiac electrograms prior to and following ablation. The Phased RFA system includes a 15" color monitor display for viewing system and ablation parameters.

Phased RFA of the pulmonary vein is an approved treatment for paroxysmal, persistent, and permanent atrial fibrillation in Europe. The Medtronic CE-Marked PVAC GOLD® (Figure 3-1) is a multi-electrode catheter used to map, ablate, and verify isolation of the PVs. In combination with the GENius generator (Figure 3-2), this phased array system can deliver RF energy to isolate PVs via creation of circumferential lesions. PVAC GOLD is a line extension of its predecessor PVAC® with three design modifications. PVAC GOLD was developed to provide a catheter with improved thermal properties with efficient energy delivery and cooling while maintaining equivalent safety and performance to PVAC. PVAC catheter is currently phased out and replaced to PVAC GOLD catheter.
A series of secondary catheters are available within the Phased RFA portfolio. These catheters are designed to create endocardial lesions in other anatomical regions of the left atrium that may be arrhythmogenic, especially in persistent atrial fibrillation. The MAAC catheter (Figure 3-3), is designed to

map and ablate complex fractionated atrial electrograms (CFAEs) throughout the left atrium. The MASC (Figure 3-4) catheter is designed to ablate CFAEs on the atrial septum. Like PVAC GOLD, these catheters simplify the creations of these specialized lesions by creating multiple lesions simultaneously, without the need for a complex 3D mapping system.

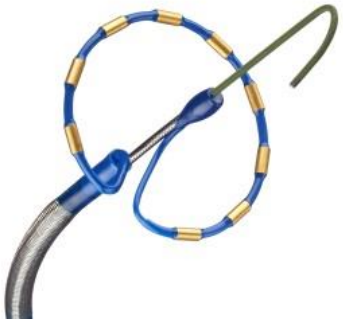


Figure 3-1: Pulmonary Vein Ablation Catheter (PVAC) GOLD.

Figure 3-2: GENius Multi-channel RF Ablation Generator.

Figure 3-3: Multi-Array Ablation Catheter (MAAC).

Figure 3-4: Multi-Array Septal Catheter (MASC).

Other:

Other catheters, sheaths, trans-septal puncture needles, and other additional devices are not specified but must be market released products.

Additional system components:

During the study duration Medtronic may incorporate new versions of generator, software, catheters when they are released by Medtronic, commercially. Information regarding product updates will be communicated to the relevant investigators in all participating sites.

3.4 Methodology

Patient can sign PIC/PDRF 14 days prior to the scheduled Phased RFA procedure to have sufficient time to consider the participation in the registry.

Observations will be documented at baseline, ablation procedure/hospital discharge and whenever patients visit the medical center with regard to AF recurrence, catheter ablations, Adverse Events, regular medical checkup etc.

Patient will be followed up for minimum 12 and maximum 14 months following first (hereafter "index") Phased RFA procedure. In case the index procedure is performed, but is not successful for medical or technical reasons, patients will stay in the registry until the end of the FU period.

Figure 3-5 provides an overview of the data entry flow chart. The process of data collection is described in Chapter 7. Furthermore, an overview of data to be collected is provided in Table 7-1.

At the baseline visit demographics, medical history, diagnostics, cardiovascular medication and quality of life (QoL) questionnaire ("AFEQT") will be recorded. During the index Phased RFA and all re-do Phased RFA procedures, related variables will be collected including: anticoagulation therapy, general procedure summary, consumables, PV isolation confirmation, adverse events (AE) assessment and hospital discharge status. During the FU period, information about in-hospital visits will be captured in the "General FU" CRFs. The "General FU" CRF contains data about arrhythmia diagnostics, symptoms, hospitalization and cardioversions (from previous visit date to actual visit), re -ablation information, cardiovascular medication, and AE assessment.

At 12 months FU, patients will be either followed up in the medical center ("12 months FU") or by phone ("12 months FU by phone"). Data recorded on the "12 month follow up" CRF is equivalent to the "General FU" CRF, with the addition of the QoL questionnaire (AFEQT). If patient has no reason to visit the medical center between 12 and 13 month after the index procedure, he might be called by study personnel and asked questions for about 15-20 min about any AF symptoms, hospitalizations, AF cardioversions since the previous visit, current medications and quality of life. Whenever12 months FU performed by phone, data received via CareLink may be used for confirmation of rhythm disturbances . The interview does not replace a medical checkup for the patient and serves as data collection only.

A delegated institution may conduct patient interview by phone for 12 months FUs at investigator's discretion. In Germany IHF is qualified to conduct 12 months FU by phone in German language. If during the study IHF is qualified for other participating countries to conduct 12 months FU by phone in other languages, this task might be extended in accordance with local laws and regulations. Should this occur, the Clinical Trial Agreements as well as in PIC/PDRF would be amended and re-submitted for approval as per local requirements.

After patient visit the medical center between 12 and 14 months follow up or after the phone follow up interview, their participation in the study is finished.

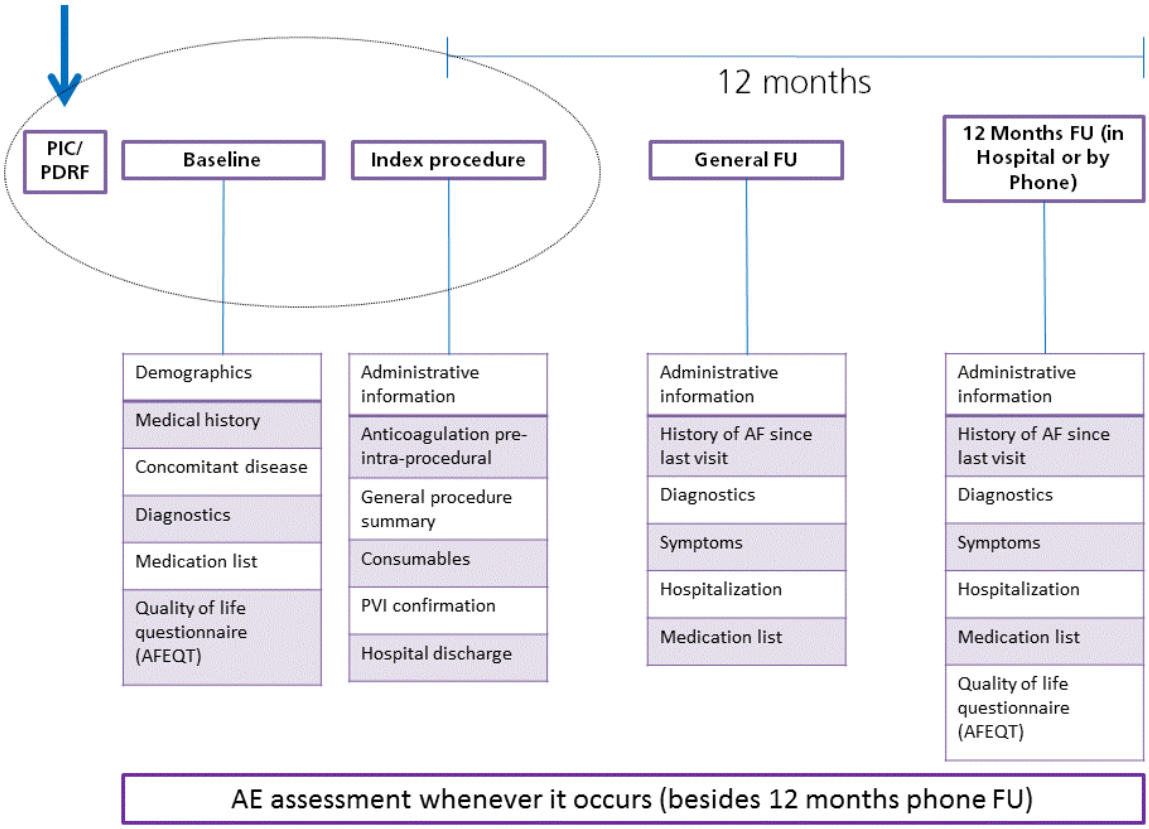


Figure 3-5: Data entry flow chart.

3.5 Quality of Life Questionnaire

Quality of life will be captured using the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire. It is a standardized, disease-specific, reliable and responsive measure of health-related quality of life in patient with AF (17). The AFEQT is a self-reported questionnaire with responses on a 7-point Likert scale. The 20-item instrument is divided into three domains (4-item symptom score, 8-item daily activities score, 6-item treatment concerns score) plus two treatment satisfaction questions. The domains symptoms, daily activities and treatment can be aggregated into an overall score.

The AFEQT has been developed as a self-administered questionnaire for patients with AF. Reading and understanding the questionnaire in the applied language is mandatory when completing the instrument (18). The AFEQT questionnaires should preferably be signed off by the patient, but if it is not possible to obtain the signature of the patient, it is accepted that a member of the site study team signs and dates the questionnaire to confirm their validity. If the questionnaire is administered by phone, the person conducting the follow up call should sign off the questionnaire.

The validated languages cover the following: French, German, Italian, Spanish (Spain), Polish and Dutch, Korean. The AFEQT questionnaire will be applied to all patients, either in the linguistically validated country-specific version or, if a country-specific validated version does not exist, in the not validated version translated into the local language of the respective patients according to local requirements and regulations. To avoid possible confounders, all analyses regarding the AFEQT questionnaire will be performed for the overall sample and stratified by validated vs not validated version.

This also applies to the mode of questionnaire administration: In general, the AFEQT questionnaire will be filled in by the patient himself. However, in some sites the AFEQT questionnaire will be administered by telephone interview. To avoid possible confounders, all analyses regarding the AFEQT questionnaire will be performed for the overall sample and stratified by self-administered vs administered by telephone interview.

The license for using the questionnaire in local languages of participating countries will be obtained and submitted under the request.

It is recommended that the questionnaire be completed at baseline and at 12 months FU. At baseline AFEQT can be completed starting from 14 days prior to the hospitalization for the index Phased RFA procedure if patient consent his/her participation in the registry.

3.6 Participating Sites

Approximately 38 sites in 13 countries (Germany, Netherlands, United Kingdom, Hungary, Italy, Spain, Switzerland, Israel, Poland, Portugal, France, Greece and South Korea) are anticipated to take part in the registry. Centers in other countries may be added during the study as well as listed countries can decline participation during the study. The list of participating sites will be updated and distributed under the separate cover.

Site eligibility for participation includes hospital-based physicians treating AF patients with Phased RFA technology.

Prior to performing study-related procedures, the site must have ethical committee (EC)/institutional review board (IRB) and associated regulatory authority approval, if applicable (e.g. Competent Authority approval), sign Clinical Trial Agreement as well as receive documentation from Medtronic or delegated CRO confirming the site readiness.

3.6.1 Site selection

The site should have adequate resources, facilities and equipment needed to follow the clinical investigational plan (CIP). The patient population should be adequate to make a contribution to the study.

Sites must have employed at least one English-speaking person, who will participate in the study and be available for all study related communication, e.g. email communication, possibly remote monitoring (see chapter 7.5.). Additionally, sites must acknowledge and agree to comply with applicable regulatory and local requirements governing clinical study conduct.

Sites will not be preselected by experience working with Phased RFA technology and RFA utilization in general. To take different sites characteristics into consideration the sites will be asked to specify their experience with Phased RFA during three years prior to enrollment as well as average range of overall RFA per year in a short site questionnaire before starting the enrollment.

The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation in addition to ensuring data integrity and the rights, safety and well-being of the patients involved in the clinical investigation.

3.6.2 Site activation

During the activation process (prior to patient enrollment), Medtronic or CRO will train site personnel on the clinical investigational plan (CIP), relevant standards and regulations, patient informed consent/patient data release form (PIC/PDRF), and on data collection and reporting tools. The site activation can be conducted in person, via telephone or remote video conference.

Sites are required to notify Medtronic of the addition of new hospital staff involvement in the study, including notification of appropriate changes in the Delegation Task Log. New study participants should be trained on the applicable study requirements relevant to their role before contributing into the clinical study. It is the site PI's responsibility, that new study personnel are comprehensively trained with regards to GOLD AF registry requirements. Trainings of all participants will be documented and signed in the Training Log file.

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following:

- EC/IRB approval (and voting list, as required by local law) of the current version of the CIP and PIC/PDRF
- Regulatory authority approval or notification (if required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Curriculum Vitae (CV) of PIs
- Documentation of delegated tasks in the Delegation Task Log
- Documentation of study training in the Site Training Log

In order to obtain database access details, the database User Account Request Form should be signed by personnel delegated to work with eCRF. A scanned copy needs to be sent to the sponsor or designee.

Additional requirements imposed by the EC/IRB and regulatory authority shall be followed, if appropriate.

Medtronic or CRO will provide each study center with documentation of study center/investigator readiness; activation letter must be received prior to patient enrollment.

4 Statistical Methods and Planned Analysis

This section describes the most relevant parts of the statistical analyses planned for this registry. All planned statistical methods will be described in detail in the Statistical Analysis Plan (SAP), which will be finalized prior to the first database freeze lock.

In general, this registry is intended to collect data under real life conditions. The statistical analysis will be performed in explorative and descriptive manner, i.e. no pre-specified hypothesis testing.

4.1 Registry Population

Data from all patients who are enrolled in the study (patients who meet the eligibility criteria and have signed the PIC/PDRF) will be included in the analysis. If a patient exits from the study, data collected prior to the study withdrawal will be included in the analysis.

4.2 Missing Data

In order to assess the effects of patients lost to follow up, percentages of dropouts will be summarized. In addition, baseline characteristics of patients who were lost to follow up in comparison to patients with a complete follow up will be described.

All reasonable attempts will be undertaken to ensure completeness of data collection in this registry. Before database lock, as many queries as possible will be cleared.

Missing data will not be imputed.

4.3 Sample size considerations

The sample size determination has been based on chronic efficacy, freedom from AF recurrence at 12 months. The sample size calculation is based on the main objective to document real-life mid-term efficacy of patients with atrial fibrillation who have undergone Phased RFA. Efficacy in this case is assumed as the proportion of AF recurrence within 12 months following the index procedure.

The table below shows the sample size needed for estimating a binomial proportion for given prevalence with corresponding precision.

Table 4-1: Table for precision and prevalence for sample size assessment.

	Precision			
Prevalence	**1%**	**2.5%**	**5%**	**10%**
0.1	4150	665	167	42
0.2	7377	1181	296	75
0.3	9682	1550	388	98

Precision = half-width of a 95% Confidence Interval (CI)
Design effect = 1.2 (variance inflation due to cluster sampling design)
Low sampling rate assumed to have no impact on sample size calculation

Assuming a prevalence of 20% of re-ablations 12 months after treatment, a sample size of 800 will allow the study to estimate the prevalence with a given precision of $\pm$ 3.8% [range of 95%-CI: 7.6%]. This size guarantees enough information for estimating the prevalence in smaller subgroups (e.g. subgroup with a prevalence of 25% with a precision of $\pm$ 6.6% [range of 95%-CI: 13.3%]).

A drop-out rate of 25% is assumed, i.e. an estimated drop-out rate of 200 patients. Therefore, it is planned to enroll a total number of patients of approximately 1000.

4.4 Statistical Methods

All variables collected in the CRF as well as the data obtained from the QoL assessments and all derived parameters will be used in the statistical analysis.

Binary, categorical, and ordinal parameters will be summarized by means of absolute and percentage numbers within the various categories.

Numerical data will be summarized by means of standard statistics (i.e. number of available data, number of missing data, mean, standard deviation, minimum, median, maximum, lower and upper quartile). In addition, adequate graphs (e.g. bar charts, box-whisker plots) may be presented to summarize the results for some parameters.

Time-to-event variables are planned to be analyzed via a Cox proportional hazard regression model presenting hazard ratios and the corresponding 95%-CI. In addition, Kaplan-Meier curves may be presented for these variables. Two-sided 95%-CI will be presented for important parameters, but should be interpreted in an exploratory descriptive way. No formal statistical tests are planned within the statistical analysis.

When all patients enrolled have exited the study, a biometrical report including descriptive statistics of all documented parameters will be generated for the overall patient population as well as for each participating country or region. Patients violating any inclusion criteria will be identified and documented. Depending on the variable(s) of interest, additional selection criteria for subjects (e.g. sub-group analyses) considered in specific analyses may be used, if considered useful during the statistical analysis.

Interim analyses, based on study data reported prior to the final report, may be completed and utilized for publication. No adjustments for alpha are necessary as no hypotheses are being tested.

Any change to the data analysis methods described in the CIP will require an amendment only if it changes main and additional objectives of the CIP. Any other changes to the data analysis methods described in the CIP, and the justification for making the change, will be described in the Statistical Analysis Plan.

The statistical analysis will be performed using SAS (release 9.3 or higher; Cary, NC, USA).

4.4.1 Statistical methods for the main objective

Estimate Phased RFA 12 months success rate

Rational: Previous studies have demonstrated that Phased RFA with the predicate platinum electrode catheter, PVAC, effectively isolates PVs with an average chronic efficacy of 74% with average follow up of 10 months. The Phased RFA literature meta-analysis published by Andrade, et al (19) reported comparable chronic success (6 months FU) was reported as 81.4% and 54.1% for paroxysmal and persistent AF, respectively.

The clinical effectiveness of PVAC GOLD catheter has yet to be estimated in PMR observational studies to establish if prospective interventional studies outcome is reproducible in daily clinical practice.

Main observational criteria: Success rate estimated as the time to first AF recurrence and/or left AfI and/or AT event from the index procedure. Data about AF events will be collected since the index procedure, including 90 days of the "blanking period" and closes at 12 months FU. If no AF/left AfI and/or events occur during the entire follow up period, 12 (+2) months, the case is considered to be "event-free".

End point definition:

1. AF pharmacological and/or electrical CV
2. AF and or left AfI more the 30 sec on ECG/EGM
3. AF less than 30 sec in combination with AF symptoms
4. Re-ablations for AF
5. Ablations for left AfI or left AT

Analysis Methods: Freedom from AF recurrence at 12 months will be estimated using Kaplan-Meier methods. A point estimate at the date of 12 months FU post procedure will be presented. Standard error will be approximated using Greenwood's formula, and a two-sided 95% log-log confidence interval will be presented. Day 0 is defined at the date of index procedure. For patients with an AF recurrence, follow up time will be set to the date of recurrence. For patients without a reported AF recurrence, those patients will be censored at the last study contact date.

Limitations: Time to first AF recurrence has practical advantages as a primary endpoint, but does not accurately reflect clinically important parameters such as the frequency, type, and duration of AF recurrence and the overall AF burden. Above known, that significant percentage of patients has silent (or asymptomatic) AF and even more, the tendency to convert symptomatic form AF to asymptomatic after PVI.
Strategies regarding the screening and management for this type of arrhythmia vary widely and are not always consistent with the few existing evidence-based recommendations.

4.4.2 Statistical methods for additional objective

Estimate Phased RFA procedure safety

Rational: Phased RFA was shown as a safe ablation technology. Andrade, et al., reported a safety profile in the meta-analysis with a complication rate of 2.0%, including an 0.63% incidence of thromboembolic complications (20). Recently a large survey (21) on RF ablation of AF has been published. It has evaluated 2,748 patients (620 with persistent AF) from 20 European centers using the Phased RFA system. The overall complication rate was 3.9%, with a stroke and TIA incidence of 1.1%.

Twelve comparative or randomized studies have been published comparing platinum electrode catheter PVAC versus alternative conventional RF ablation catheters. Briefly, all studies demonstrated equivalent safety outcomes. The novel catheter design of the PVAC GOLD array may improve safety by reducing embolic events as it prevents electrode 1-to-10 interaction and allows for enhanced tissue contact due to the 20° forward tilt. This registry will collect information about complication rates linked to the Phased RFA system or to the procedure itself.

Major procedure related complications include vascular complications secondary to venous access, cardiac tamponade, embolic stroke, esophageal injury, phrenic nerve injury, PV stenosis, and reentrant tachycardia arrhythmias arising from ablations, mainly left Afl.

Endpoint Definition: Procedure-related and/or device-related adverse events as determined by investigator.

Analysis Methods: The number of patients with reported device and procedure related events will be summarized as a binomial variable; number and percentage of patients with events. Additionally, a Kaplan-Meier estimations will be used to summary the timing of the occurrence of safety events through 12 months. Time from onset to resolution of events may also be presented.

Measurements: Adverse events to be documented starting from the index procedure until the 12 months FU.

4.4.3 Statistical methods for ancillary objectives.

Characterize the acute procedural success rate

Rational: A cornerstone of the ablation procedure is to block electrical conduction from the PVs. According to guidelines (22) both, exit and entrance block, are equally accepted as confirmation of PVI and used as indicator of acute success.

In previous studies with Phased RFA an average acute procedural success of 98.2% (93-100%) was reported in patients with paroxysmal AF (23 studies).This is similar to the average acute procedural success reported for patients (6 studies) with persistent AF of 96.3%. In the case of index procedural failure, the authors linked the failure to the patient anatomy or characteristics and not to the Phased RFA system.

Endpoint definition:

- Procedure attempt was not declined due to technical issues related to Phased RFA system
- Only PVAC catheter(s) used to achieve PVI
  AND
- All accessible PVs were isolated (entrance and/or exit block confirmation per vein)

If exit or entrance block was not verified during the procedure the data will not be used for this analysis.

Analysis Method: Acute procedural success rate will be reported as frequency and percentage at both the patients and vein level. Acute procedural success rate by patients will be calculated as number of patients with acute procedural success divided by number of patients with an attempted Phased RFA procedure. Acute procedural success rate by vein will be calculated as number of veins with electrical isolation verified divided by number of veins attempted with Phased RFA. 95% confidence intervals will be calculated using Fisher's exact method.

Limitation: Even though PVAC GOLD catheter has been designed anatomically, steerability can be influenced by the sheath used with the catheter. With fixed curve sheath might become challenging to reach all PVs, in particular right inferior PV due to technical issues. Due to this additional use of 3D system and irrigated catheters might be utilized by the medical centers where steerable sheath is not available.

Assess Phased RFA efficiency

Rational: The multi electrode catheter technology delivers continuous lesions and shortens procedure times. The ability to map and ablate with the same electrode simplifies and shortens the procedure.

Procedure duration is impacted by the maneuverability of the catheter. The new catheter design of the PVAC GOLD array allows enhanced tissue contact due to the 20° forward tilt.

Hospital resource allocation is another indicator of procedural efficiency, reflected by the procedure duration ("from skin to skin"), laboratory occupancy ("from door to door"), fluoroscopy time as well as number of used catheters and adjunctive devices (mapping and navigation) used.

Endpoint definition:

- Total lab occupancy time is defined as time patients enters the EP room to time patients' is out of EP room.
- Total procedure time is defined as time of first venous access to time of last catheter removal.
- Total fluoroscopy time is defined as time of elapsed fluoroscopy time at time of first catheter insertion to elapsed fluoroscopy time at time of last ablation catheter removal.
- Left atrium dwell time is defined as time from first Phased RFA catheter insertion to last Phased RFA catheter removal.
- Total Phased RFA time is defined as the sum of durations in which Phased RFA catheter is applied to pulmonary veins.
- Adjunctive devices: additional use of non-Phased RFA catheters, mapping or navigation systems to achieve PVI
- Adjunctive devices (mapping or navigation systems)

Measurement: Will be taken during the Phased RFA procedure.

Analysis Methods: Procedure parameters including procedure times, number of applications, duration will be summarized using n, mean, SD, minimum, median, or IQR, minimum and maximum. Parameters may be presented as summaries by patients and by pulmonary vein.
Limitations: no limitations are known for these parameters.

Characterize the peri -procedural anticoagulation therapy

Rational: Two known complications that occur during or shortly after the procedure: thromboembolic events including stroke and major bleeding including cardiac tamponade, with an estimated incidence of 1.33% and 0.94%, respectively (23). The combination of heightened risk of both stroke and hemorrhage is linked to the complexity of the AF ablation procedure and the need for adequate peri-procedural anticoagulation. Historically, peri-procedural warfarin therapy was discontinued and replaced with bridging low-molecular-weight heparin (LMWH) before and after the ablation, followed by resumption of warfarin at hospital discharge. Although widely adopted throughout the world and endorsed by current guidelines, it was recognized that this approach may result in a higher incidence of bleeding complications, especially at the site of vascular access (24). Several studies have suggested that continuation of therapeutic warfarin could reduce thromboembolic complications without increasing the risk of hemorrhagic complications (16, 25, 26). However, international normalized ratio (INR) levels often fluctuate during warfarin use, and may not be in the optimal therapeutic range in up to >50% of patients (27). Lower or higher INR levels on the day of ablation may increase the risk of complications. Novel oral anticoagulants (NOACs) are used as an alternative to chronic warfarin for stroke prophylaxis in patients with non-valvular AF. They have fast therapeutic effect without need for INR control and obviating the need for bridging heparin.

The registry will collect data about anticoagulation therapy for Phased RFA and correlate it with the peri-procedural thromboembolic events and bleeding.

Endpoint definition:

- Activated clotting time (ACT) during the procedure
- Peri-procedural INR
- Oral anticoagulant therapy/LMWN before, during and after the procedure
- TIA/stroke related to study Phased RFA procedure

Analysis Methods: Oral anticoagulation medication will be displayed before, after and for each procedure and for the FU. Frequency distributions (counts and percentages) will be presented for each point in time and changes in anticoagulation will be displayed. ACT and peri-procedural INR will be displayed by descriptive statistics (n, mean, SD, median, IQR, minimum and maximum). TIA/stroke event rates related to phased RFA procedure during the first three days after procedure will be calculated using Kaplan Meier estimates.

Describe single catheter PVAC GOLD utilization in persistent AF

Rational: Ablation of persistent AF is a challenging and long procedure with varying success rates (7). There is a significant variety of AF forms covered by the definition "persistent AF". According to current European guidelines persistent AF is defined as AF that persists without interruption for 7 days or longer. Whenever patients have been cardioverted during the first 7 days of an AF episode should be classified as persistent one. A single CV later than 48 hours from arrhythmia onset turns a patient with paroxysmal AF into a persistent one and has to be distinguished from the patient with AF episodes for weeks or months which never terminate spontaneously. Above the limited clinical ability to discriminate paroxysmal and persistent AF, the success rate of ablation for persistent AF can vary significantly, which may be due to large structural and electrical remodeling that occurs in the LA between early persistent AF and long-standing persistent AF (28). The Phased RFA meta-analysis reported 54.1% chronic success among persistent AF patients (19). It was shown that utilization of MASC and MAAC catheters for complex fractionated atrial electrograms additionally to PVI lead to 66% long-term success rate in persistent (14) and 49% in longstanding persistent AF (29), respectively. However, recent results from the STAR AF II study have shown that additional linear or focal lesions do not improve efficacy compared to PVI alone (8). The maintenance of sinus rhythm is not dramatically different between 'persistent' AF patients undergoing PVI alone compared with patients undergoing more extensive ablation approaches, including a risk to develop left atrial tachycardia. Until now it is not possible to tailor precisely an ablation strategy to persistent and longstanding persistent AF. It is a point of interest for the registry to evaluates which tools and consumables participating centers use in persistent and long standing persistent AF and to verify patients' characteristics, procedure approaches and estimates mid-term outcome across participating sites.

Endpoint definition:

- Describe % of patients with persistent vs paroxysmal as an indication for Phased RFA at baseline
- Describe if additional substrate modification (liner lesions, CAFÉ ablation) were performed above PVI

Analysis Methods: respective subgroup analysis can be considered for patients:

- With persistent versus paroxysmal AF.
- Treated with the PVAC GOLD catheter only in persistent AF patients

Evaluate QoL (AFEQT) dynamic through 12 months.

Rational: Symptom relief and improvement in QoL are the major therapeutic goals of PVI. The validated AFEQT questionnaire designed specifically to assess the impact of AF burden on patient's QoL. Improvement in QoL will be used as a subjective indicator of Phased RFA long term success.

Endpoint definition: AFEQT questionnaire completed at baseline and at 12 months FU.

Analysis Methods: Change in QoL from baseline to 12 months will be summarized using mean, SD, minimum, median, maximum and IQR. Statistically significant change from baseline will be assessed using a two-sided t-test.

Limitations: If QoL was completed at baseline, but missed for 12 months FU, this patient will be excluded from the analysis. As far as QoL is not a standard of care in some hospitals it is up to patient consideration to complete or to refuse QoL completing.

5 Project Termination

5.1 Premature termination or suspension

Premature termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single site.

The sponsor reserves the right to close prematurely the study without reaching the anticipated sample size due to unexpected reasons (i.e. slow enrollment rate). In such cases, all data collection will terminate and after sponsor receipt of the data collected prior to termination, the participating physicians will be compensated as agreed upon contractually.

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process
- Slow enrollment rate, which does not allow to reach the anticipated sample size

a) PI/site

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

- Failure to obtain initial EC/IRB approval or annual renewal of the study
- Persistent non-compliance to the CIP
- 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.)
- EC/IRB suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- PI request (e.g. no longer able to support the study). The PI shall then promptly inform Medtronic and applicable EC/IRB and regulatory authorities, if applicable.

b) Patient

- Patient chooses to withdraw his/her PIC or PDRF consent
- Death

5.1.1 Procedures for Termination or Suspension

5.1.1.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC and the institution (where required per regulatory requirements)
- In the case of study termination, the investigator must inform the patient, or legally-authorized designees or guardians and may inform the personal physician of the patient to ensure appropriate care and follow up is provided
- In the case of a study suspension, patient enrollment must stop until the suspension is lifted by Medtronic

5.1.1.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the site (where required per regulatory requirements)
- The investigator will promptly inform the EC and regulatory authority (where required per regulatory requirements)

- The investigator will promptly inform the patient, and may inform personal physician of the subjects to ensure appropriate care and follow up is provided

5.1.1.3 EC-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Patient enrollment must stop until the suspension is lifted
- Patient already enrolled should continue to be followed in accordance with EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, and may inform the personal physician of the patient, with the rationale for the study termination or suspension
- The investigator will inform local regulatory authority, where required per regulatory requirements

5.2 Planned study closure

Study closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the final report or after final payments, whichever occurs last. The responsible EC/IRB and regulatory authorities, if applicable, will be notified according to local regulations.

6 Patient Consent to Release Information, Ethical Review and Regulatory Considerations

6.1 Patient Consent to Release Information

This in an observational study and does not impose any form of intervention by the investigator. Hence, the assessment and treatment of patient are based solely on the physician's routine or usual practice in the provision of care to subjects with AF. Therefore, the participating patients will provide authorization for the uses and disclosures of their personal health information as described in the Patient Informed Consent (PIC) or Patient Data Release Form (PDRF). The PIC/PDRF covers the collection and release of data regarding treatment and its outcomes for the entire period of the study from all health care providers. The confidential nature of the patient information will be maintained in accordance with European laws and regulations. For the purpose of the phone FU, the patient's contact information needs to be saved. It will be secured separately from the medical data and only designated, trained and delegated study staff will have access to this information. A delegated institution (IHF GmbH, Ludwigshafen) can conduct the FUs up to PI consideration. The patient will be informed accordingly in the PIC/PDRF and ask to sign for his/her consent.

During the consent discussion the PI or his/her designee must fully inform the patient of the study using non-technical which is understandable for the patient. The patient must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient. When the patient decides to participate in the study, the written PIC/PDRF must be signed and personally dated by the patient and the investigator. After all persons have signed and dated the PIC/PDRF the investigator must provide the patient with a copy of the signed and dated PIC/PDRF.

6.2 Risks and Benefits

All therapies and diagnostic methods used in this study are based on commercially released devices.

Since the products will be used in accordance with their labeling, it is not anticipated that patients enrolled in this study will be exposed to any risks beyond those, normally associated with Phased RFA procedure.

Patients are treated according to standard hospital practice. No extra tests and FUs at the sites are required. Therefore, no additional risks are associated with participation in this study.

There are no direct personal benefits for participating patients.

Participation in the study will contribute to a better understanding of the performance of the Phased RFA system. The information gained from this study could result in improved management of patients undergoing ablation with the Phased RFA system and may be important for future therapy developments and future treatments.

6.3 Ethical Review and Regulatory Consideration

The study will be conducted according to the Declaration of Helsinki 2013 (30), this Clinical Investigational Plan (CIP), national and local laws, regulations, standards, and requirements of the countries where the study is being conducted, including data protection laws.

In addition, to follow the governing regulations noted above, any additional requirements of the individual study center's EC/IRB or regulatory authority will also be followed by the study center where applicable.

All required regulatory notifications / approvals for non-interventional studies will be followed according to each country.

The GOLD AF Registry was designed to reflect the GCP principles, including the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The international ethical and scientific quality standards and principles of the Declaration of Helsinki 2013 (30) and later versions throughout the study and the good clinical practice (GCP) (31) are implemented in this study by means of the Patient Informed Consent (PIC) process, EC/IRB approval, study training, clinical trial registration, risk benefit assessment, publication policy, etc. The study will be conducted according to national and local laws, regulations, standards, and requirements of the countries / geographies where the study is being conducted and the Clinical Investigation Plan (CIP), Clinical Trial Agreement (CTA) at each participating site.

This study will be publicly registered (see chapter 9).

GOLD AF registry will be submitted to EC/IRB/CA for approval/notice if required by local law. In addition, Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ECs/IRBs and regulatory authorities as required by local laws and regulations.

The Sponsor will avoid improper influence on or inducement of the patients, monitor, any PI(s) or other parties participating in, or contributing to, the study. All PIs shall avoid improper influence on or inducement of the patients, sponsor, monitor, other PIs or other parties participating in or contributing to the study.

6.4 Amendments to the CIP

Medtronic and/or designee (CRO) will submit any amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities and to the PIs to obtain approval from their EC/IRB, if applicable. Furthermore, Medtronic and CRO study management and shall provide review and approval of each amendment, as applicable according to the function in the study.

6.5 Data Protection

All records and other information concerning patients participating in this study will be treated as confidential. Patients' data will be stored and processed in pseudonymized form, i.e. without referencing patients' name or initials. An identification number assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when analyzing and reporting registry-related data. Study data may be transferred to the United States of America and other countries' entities for processing. However, the patients' privacy will be maintained according to the requirements of Data Protection Directive 95/46/EC and national legislation for data protection.

Authorized personnel (hospital and specialized site staff, representatives of the Sponsor and CRO) will have access to personalized patient data in original source documents (medical records). Patient will agree to this by signing patient informed consent or data release form.

6.6 Insurance and Liability

The liability of the participating physician is the same as their standard medical practice as this is an observational study. As this is an observational study, patient's insurance **statement/certificate** will only be provided if required by the local law.

7 Warranty information will be provided in the product packaging. CE certificated copies are available upon request. Recording Keeping, Data Reporting, and Data Quality Assurance

Data quality assurance will include handling rules for missing or incomplete data, and range checks (i.e., age, date, etc.), along with data transformations. Data quality checks will be described in the Data Management Plan.

The PI will comply with the confidentiality policy as described in the CTA. He/she will comply with the CIP (which has been notified or approved (if applicable)) by the respective EC/IRB and the requirements described in the CTA between Medtronic and the site. The PI is ultimately responsible for the conduct of all aspects of the registry at the participating site and verifies by dated signature the integrity of all data transmitted to the sponsor.

7.1 Data Collection Procedure

Data will be collected via electronic case report forms (eCRFs) via a web-based study database using the software solution EBogen©, developed by the IHF GmbH, Ludwigshafen, Germany.

The GOLD AF database is reachable over the following link: http://studien.herzinfarktforschung.de/goldaf.

Case report forms for this study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data system after the site has fulfilled all requirements for database access.

Data will be stored in a secure, password-protected database which will be backed up hourly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated by the sponsor (and/or CRO) to monitor data quality and study progress. The investigator is responsible for the oversight (review and signature) of the eCRFs.

At the end of the study, the data will be frozen and retained and will be retained per sponsor policy.

Prerequisites for using the EBogen© system include, internet access using a current web browser (Internet Explorer 8 or later, Firefox, Chrome or Safari) supporting JavaScript. No local software installation is required.

7.1.1 Data collection

The PI must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified by a documented rationale, signed and dated by the site investigator, to be entered in the EBogen© system. Only authorized persons can complete eCRFs. eCRFs shall be signed by PIs as specified on the Delegated Tasks List included in the Investigator Site File (ISF). All efforts should be made to complete 100% of data collection of required variables.

7.1.2 Data review and processing

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the respective PI to complete, correct or comment the data.

In order to document that the site has completed data entry for an EBogen section, they have to be signed by the authorized personal.

If any changes are needed in the CRF, signature can be revoked by investigators and /or authorized personal with specifying the reason of signature revoke (e.g. need to add data, need to correct data etc.). After changes in the CRF it should be signed again as a completed one.

All efforts should be applied by the participating site staff to answer 100% of site queries.

7.2 Data collection process

All follow up (FU) visits in this registry will be performed in accordance with standard of care in participating medical centers.

Data from "routine" FUs should be reported in "General FU" case report form (CRF). If a patient visits the medical center within the period 12-14 months after the index Phased RFA, this data should be documented in the "12 months in hospital FU" CRF, which contains the QoL questionnaire, additionally to the "General FU" information. If "12 months in hospital FU" was completed in the database, no further FU visits are required, and the patient exits the study. "Exit form FU" CRF is not required.

If after 12 (+1) months from the procedure the "12 months in hospital FU" CRF was not completed in the database, study personnel will receive a notification to conduct 12 months FU by phone and fill in "12 months phone FU" CRF. Therefore "12 months in hospital FU" CRF can be completed within 12 - 14 months after the index Phased RFA. Between 13 and 14 months after the index Phased RFA either "12 months in hospital FU" or "12 months phone FU" CRFs (whatever occurs first) can be completed (Figure 7-1).

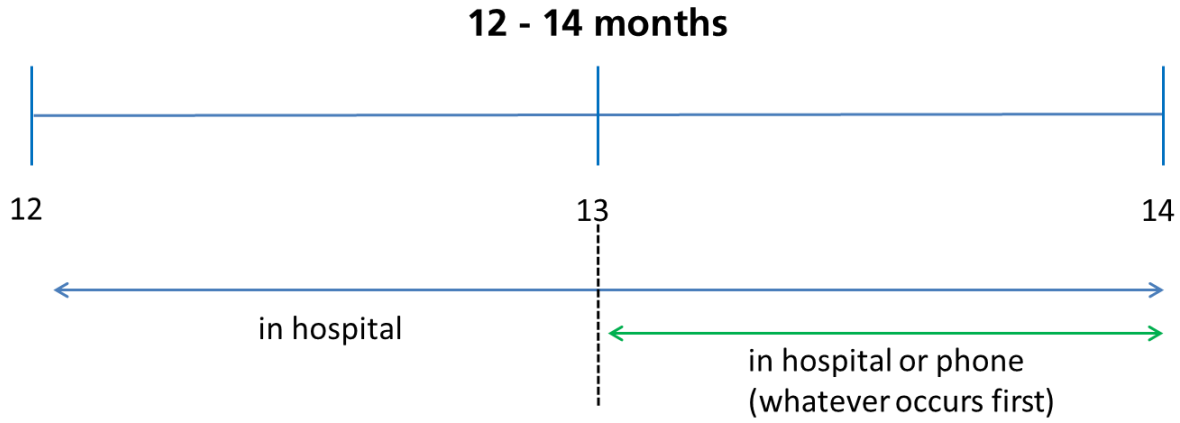


Figure 7-1: 12 months FU management.

Enrollment

A patient is eligible if he/she meets the eligibility criteria described above. Enrollment of a patients is complete once consent (PIC/PDRF and/or authorization/privacy form) has been obtained.

Patients can be enrolled starting from 14 days prior to the hospitalization for the index Phased RFA procedure, as well as during the hospital stay.

Baseline

The baseline visit can occur the same day as enrollment, however, consent should be obtained prior to any data collection.

The "Baseline" CRF will be used to collect demographic data, primary indication for Phased RFA, cardiovascular diseases history, arrhythmia status, history of AF, symptoms, concomitant diseases, diagnostics, cardiovascular medication. QoL questionnaire "AFEQT" will be completed by the patient and data transferred to eCRF.

Procedure visit

The procedure will be performed according to the hospital's standard Phased RFA practice.

The "Procedure" CRF will be used to collect data about the ablation procedure and discharge from the medical center. Information regarding anticoagulation therapy, procedure summary information, sedation and consumables, PVI confirmation, cardiovascular medication, date and status at hospital discharge is to be collected. Verification of study defined AEs will be done during the procedure and at the moment of hospital discharge.

If the attempt to conduct Phased RFA ("index" procedure) is not successful for clinical or technical reason, patients will stay enrolled into the registry. If Phased RFA is repeated ("repeated" procedure) or re-do due

to arrhythmia recurrence, the "procedure" CRF should be filled in. Information about all Phased RFA attempts will be used for the analysis. If patient has re-do procedures with some other technology than Phased RFA, Procedure CRF is not required; information about technology which was used for re-ablation to be collected in eCRF "General FU".

During the Phased RFA, the investigator may require use of other commercially available devices for other ablations such as Afl/AT or other AF triggers. The use of other devices will be at the investigator's discretion and use will be documented on the eCRF.

Hospital discharge needs to be completed when the patient is discharged from the hospital, this data to be collected a as a part of the procedure visit. Information about date of discharge, reportable adverse event since the procedure and recommended medication information is to be collected. Post-ablation drug regimen is determined at clinical discretion of the treating investigator.

General Follow up visits (in hospital)

The "General" FU CRF will be used to collect data during all standard visits at the site within the following 12 months after the index or study procedure. Data to be collected include: arrhythmia assessment, diagnostics, symptoms, hospitalizations, ablation information and medication. If "General FU' will take place due to system/procedure related AE, "Adverse Event" CRF should be filled in additionally to the "General" FU CRF.

If at any moment during FU, the patient withdraws PIC/PDRF or PI receives information about the patient's death, the "Exit" CRF should be filled in addition to the "General FU" CRF. All data collected prior to the patient exit will be used for analysis, unless different is required by local laws and regulations.

12 months FU (in hospital or by phone)

If the patient appears in the participating medical center within 12 - 14 months after the index procedure, the "in hospital 12 months FU" CRF should be completed. If an "in hospital" visit does not occur after 13 months post index procedure, the site should apply all efforts to conduct interview by phone and document it in "12 months phone FU" CRF. The phone FU interview does not replace a medical checkup for the patient and serves as data collection, only.

Data to be collected during 12 months FU includes arrhythmia assessment, diagnostics, symptoms, hospitalization and re-ablations occurred since last visit, medications, QoL questionnaire.

To ensure a unified approach and to minimize possible bias, all sites will be trained to use the standardized "patient questionnaire for phone FU" with questions regarding parameters of interest equivalent to eCRF variables. In Germany, the phone FUs can be performed by Institut für Herzinfarktforschung, GmbH.

If study personnel obtain information during the phone FU that patient will appear in the hospital before the end of FU window, it is under site consideration to complete „12 months phone FU" CRF or conduct a medical check -up and complete „in hospital 12 months FU".

Study Exit

Prior to exiting a patient from the study, it is recommended to follow the patient until all ongoing reportable AEs are resolved or unresolved with no further actions planned. Upon exiting from the study, no further study data will be collected or study visits will occur for the patients. All data available through the time of the subject's exit will be used for analysis.

Patients are urged to remain in the study until the end of individual follow up but may be exited from the study for any of the following situations:

- Patient lost to follow up
- Patient chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, , failure of subject to maintain adequate study compliance)
- If patient were enrolled with the intention to perform Phased RFA, but get ablation with another technology
- Death

If patient has enrolled into study and vascular access was obtained with the intention of completing the study Phased RFA, but the subject did not receive any ablation energy, or complete entire study

procedure, sites will be asked to keep patients enrolled for 30 days to ensure potential procedure / device related AEs are assessed and collected. If there are no related.

All subject deaths must be reported by the investigator to Medtronic on an Exit Form as soon as possible after the investigator first learns of the death.

In the event of a patients's death, the investigator is responsible to assess at their own discretion whether or not the death is related to the procedure and/or the system.

If any relatedness is assesses, it is required also the completion and reporting of a Serious Adverse Event (SAE) form (see paragraph 11.1.1).Data collection requirements are summarized in Table 7-1 below.

Table 7-1: Data collection requirements at subject visits

Data Collection*	Baseline	Procedure	General FU	12 Months FU	12 Months FU by phone
Enrollment (PIC/PDRF)	X				
Demographics	X				
Medical History#	X				
Concomitant disease	X				
Diagnostics	X		X	X	X
Symptoms			X	X	X
Medication list	X		X	X	X
Administrative information		X	X	X	X
Anticoagulation pre-intra-procedural		X			
General procedure summary		X			
Consumables		X			
PVI confirmation		X			
Hospital discharge		X			
Quality of Life (AFEQT)	X			X	X
History of AF since last visit			X	X	X
Hospitalization			X	X	X
Reportable Adverse events** (AEs)	- Whenever occur -				
Study Exit	- Whenever occur -				
Study Deviation form ***	- Whenever occur -				

* prior to first patient enrollment every site needs to fill in a site questionnaire once #= Medical history includes questions about prior CVD, history of AF, main underlying disease, concomitant disease and history of AF.

** Data collecting requirement for Adverse Event eCRF described in chapter 11 "Adverse Event"

*** Data collecting requirement for Deviation eCRF described in chapter 7.4 "Study Deviations"

7.2.1 Frequency of Follow up

Data collection will be completed following standard of practice procedures at each participating site.
Most of the sites have a standard of care for post AF ablation visits to invite patients for the medical checkup after the "blanking period" which is lasts around 3 month after the ablation procedure; some sites also see patients at 6 and 12 months after the Phased RFA.

To mitigate variations in clinical care practices for analysis, the visit windows below are proposed to aligning with typical care practices for this therapy. Data analyses will include follow up visits, regardless of when they occur.

Table 7-2: Follow Up Visit Windows

Months	Window Starts (days post procedure)	Target (days post-procedure)	Window end (days post-procedure)
3 months	85	90	100
6 months	175	180	190
12 months	351	365	425

Additional data collection activities may be completed using sub-studies under the GOLD AF Registry protocol. Sub-studies may be developed to satisfy local data needs and/or evaluate additional areas of scientific interest. Sub-studies must be reviewed and approved by Medtronic and will be documented and managed under separate cover.

7.3 Source documents

Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, QoL questionnaires must be created and maintained by the investigational site team. The investigator will clearly mark clinical record to indicate that the subject is enrolled in this study. The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement, that it is a true reproduction of the original source document.

The PI and/or institution shall permit Medtronic, the CRO and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform study-related monitoring, audits, EC/IRB review and regulatory inspections.

7.4 Study Deviations

A study deviation is defined as any incompliance to the Clinical Investigation Plan or the Clinical Trial Agreement.
All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the patient in an emergency. Examples of study deviations are:

- Missing/incorrect data
- Missed PIC/PDRF sign off, incorrect PIC/PDRF version signed
- Incorrect version of the consent form provided to the patient
- CIP required training deviations
- CTA violations (e.g. enrollment started before CTA)
- EC approval not obtained before starting the study
- Patient enrolled during lapse of EC approval
- Informed consent not obtained prior to participation in the study
- Incorrect version of the consent form provided to the subject
- Enrolled subject did not meet inclusion/exclusion criteria
- Unauthorized physician or study personnel performing study procedures

Deviations from the CIP, which are outside the EBogen system, can be controlled by monitoring visits. Queries and discrepancies found at a monitoring visit will be handled according to the Monitoring Plan.

Deviations in the EBogen system are handled through emails sent to the site and might be explained within remote monitoring calls to the sites (see chapter 7.5).

Study deviations need to be documented in eCRF "Deviation Form" which contains following data:

- Administrative information (e.g. CaseNo for patient identification, site ID; date of Deviation)
- Deviation description
- Reason for Deviation
- Action taken

The eCRF "Deviation Form" can be completed by the site personnel or by the sponsor of designee in cooperation with the site personal and has to be signed by authorized site person.

Data entered in the EBogen system is checked for completeness and accuracy of data entry, directly. By default, all fields are marked as required. However, with the exception of the first page containing the stratification and eligibility questions, the navigation in the CRF is not restricted, even if fields are missing or contain invalid data. All fields that are optional have been assigned an "NA" checkbox or a similar option to specify that this field is not available. Checking this "NA" option will disable the original data entry field to signal that the value is not available. Fields that are foreseen for specific investigations (non-mandatory investigations) are only available when the leading question has been marked "yes", or the obvious corresponding choice was made. Depending on the layout and size of the fields these conditional fields will be either disabled or made invisible until the appropriate prerequisite is fulfilled.

7.5 Monitoring

It is the responsibility of the Sponsor to ensure proper monitoring of this clinical investigation per regulations. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements.
Medtronic, or delegates, must therefore be allowed access to the patients' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Subject Informed Consent, Research Authorization (where applicable) and Clinical Trial Agreement. The Monitoring Plan will be maintained separate from the Clinical Investigation Plan.

Frequency of monitoring visits will be based upon patient enrollment, duration of the study, study compliance, number of adverse events, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. The principal investigator shall be accessible during monitoring visits. Monitoring for the study will be done in accordance to the study Monitoring Plan. Site initiation and closure visits will be performed by Medtronic or designee. Monitoring visits may be conducted to assess site study progress, the PI's adherence to the CIP, regulatory compliance including but not limited to EC/IRB review and approval of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors may work with study personnel and the site's PI to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

7.5.1 . Access to study site and study materials

The PIs, his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic clinical personnel and or CRO delegate. This accessibility is of particular importance for reviewing data in the CRF. Direct access to patient records for source data verification will be granted and prepared prior to any monitoring visits.

7.5.2 Audits and study site inspections

Medtronic may choose to perform random audits throughout the study as part of quality assurance. The purpose of an audit is to verify the adequate performance of the study related activities, independently of the employees involved in the study. Regulatory bodies may also perform inspections at participating study sites.

The PI and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform study-related monitoring, audits, EC/IRB review and regulatory inspections.

In addition, when applicable, the study sites may be inspected by the competent authority. Any competent authority announcements shall be forwarded to Medtronic study management immediately. Study sites will be required to provide access to source documents and data to the regulatory bodies and competent authority.

Monitoring visits will be conducted in accordance to the Monitoring Plan.

8 Reimbursement

Compensation according to local regulations and to the time spent to inform patients and to document patient data will be paid. Reimbursement conditions will be documented in the Clinical Trial Agreement.

9 Registration

This study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki 2013 (30) on http://clinicaltrials.gov.

10 Good Clinical Practice

This registry will be conducted according to the rules of Good Clinical Practice (GCP) (31). These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct, credibility and data integrity of the clinical investigation, and the definition of responsibilities of the sponsor and investigators.

11 Adverse Events

The products used in the study are market released in all geographies and used within the current indications for use as indicated in the product labeling. Foreseeable adverse event information is provided in the product labeling documentation. The collection of adverse event (AE) for reporting will be performed according to local requirements for observational studies. To achieve the study objectives, AE data relevant to the study objectives need to be collected.

All procedure-related and system-related AEs will be collected throughout the study duration, starting at the index procedure.

AE information will be reported to Medtronic upon site awareness on an Adverse Event Form, including a description of the AE, date of AE onset and PI awareness, diagnostics, symptom's description, treatment, resolution, and assessment of both the seriousness and the relatedness to the device. For Serious Adverse Events that require immediate reporting, initial reporting may be done by phone, fax, email (see section "Directory" for Medtronic contact details), or on the CRF completing as much information as available. The original completed AE CRF must be reported to Medtronic as soon as possible. If AE is not resolved at the moment of completeness, AE update needs to be completed upon AE resolution. All efforts should be applied to follow unresolved adverse events until they has been resolved, is unresolved with no further actions planned, the patient exits the study or until study closure, whichever occurs first.

An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the investigator's opinion, including, but not limited to the list of unavoidable AEs provided in in Table 11-1.

Unavoidable AEs are not reportable AEs. Onset of any of these events occurring after the specified timeframes and/or events lasting longer than the specified timeframe if onset is at the time of the surgery need to be reported (if it is procedure or devise related AE).

Table 11-1: Unavoidable Adverse Events Related to Ablation Procedure

Name	Event Description Time Frame (Hours) from the Surgical Procedure
Anesthesia related nausea/vomiting	24
Low-grade fever (<100 F or < 37.8 C)	48
Groin insertion/site pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to lying on the table	72
Chest pain secondary to ablation (during procedure)	4

11.1 Protocol defined Adverse Events

- Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.
- Unavoidable Adverse Events, listed in Table 11-1 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-procedure.

Adverse events relevant to the clinical objectives are defined in Table 11-2.

Table 11-2: Adverse Event Definition

General (including ISO 14155:2011 definitions)	
Definition	**Description**
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patient, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Serious Adverse Event (SAE)	An adverse event that a) led to a death, b) led to a serious deterioration in the health of the patient that either resulted in • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalization, or • resulted in medical or surgical intervention to prevent permanent • impairment to body structure or a body function c) led to fetal distress, fetal death or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (ISO 14155:2011 3.15) NOTE: Device deficiencies include malfunctions, use errors, technical observations and inadequate labeling.
Adverse Device Effect (ADE)	Adverse Device Effect (ADE): adverse event related to the use of an investigational medical device. Note 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunction of the medical device. Note 2: This definition includes any event resulting from user error or from intentional misuse of the medical device (ISO 14155:2011, 3.1)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2011, 3.42)

Study required (reportable) AEs	
System Related AE	An adverse event that results from the presence or performance (Intended or otherwise) of the Phased RFA system component. • Catheter Related: An adverse event that results from the presence or performance (intended or otherwise) of the Phased RF catheters • Generator Related: An adverse event that results from the presence or performance (intended or otherwise) of the Phased RF generator Note: ISO defined ADE is part of Serious System related AEs.
Procedure Related AE	An adverse event that occurs due to index or Phased RFA re-ablation procedure. • Phased RFA Procedure Related: Event that occurs due to any procedure related to the Phased RFA procedure. • Procedure Related: Event that occurs due to any other procedure during the Phased RFA in the study (e.g. EP study, ICM implant).
Serious system or procedure related AE	An AE which full fill the definition of the procedure or system related AE combined with definition of seriousness (see above SAE). Note: ISO defined SADE and USADE are part of Serious system related AEs.

Reporting of ALL Serious Adverse Events is not part of the GOLD AF registry. Nevertheless, all geography specific AE reporting requirements (EC or regulatory reporting) should be followed. It is the responsibility of the PI to comply with any AE reporting requirements stipulated by EC/IRB with the applicable support provided by the sponsor.

AEs will be reviewed by Medtronic. This review will include the determination whether the AE meets country regulatory requirements. The sponsor will ensure timely AE reporting to meet global regulatory requirements.

11.1.1 Patient Death

Death classification:

1. Phased RFA system related
2. Phased RFA procedure related
3. Not study related

As soon as possible after the investigator first learns of the death, the CRF "Exit form" needs to be completed and the classification provided as per above.

In case the death is related to the Phased RFA system or Phased RFA procedure, a CRF "Adverse event" needs to be completed as a serious AE.

Regulatory reporting of the patient's death will be completed according to local regulatory requirements.

11.2 Vigilance Reporting

All devices used in this study are market-released. Therefore, Post Market Surveillance and product complaint reporting is applicable to all market-released devices used in the study. The reporting of product complaints abuse, and misuse of these CE-labeled devices is not part of the study and should be done in addition to the AE reporting according to regional requirements.

11.3 Adverse Events Advisory Committee (AEAC):

At regular intervals, an independent Adverse Events Advisory Committee will conduct a medical review of the AEs for adjudication. The Committee will consist of a minimum of three non-Medtronic employed physicians that are not participating investigators for the study, including the AEAC chairperson.
The AEAC is responsible for reviewing the investigator's assessment and classification of AE. The AEAC will review AEs and provide a final adjudication of relatedness and seriousness and can advise on the provided diagnosis.
For seriousness only study reportable AEs will be adjudicated. Relatedness of the AEs can be adjudicated as not related to the procedure/system or classified according to the Table 11-2.

Study lead may facilitate and participate in AEAC meetings, but will be non-voting members. The safety Medtronic personnel or study manger will provide the AEAC with the PI's description and classification AEs under review.
If the AEAC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the AEAC, this will be documented accordingly. If the investigator does not agree with the AEAC classification, both determinations will be documented within the study report. However, the AEAC determination will be used for analysis purposes.

11.3.1 Device Deficiencies

Device deficiency information is not to be collected throughout the study, though can be adjudicated by the aforementioned AEAC.

12 Legal Requirements

This registry fulfils the requirements of the Directive 2001/83 EC, title IX and Volume 9A of The Rules Governing Medicinal Products in the EC, the Declaration of Helsinki 2013 and later versions throughout the study (30) and will be conducted in accordance with the respective SOPs of Medtronic and CRO (IHF). The applicable SOPs for the study will be determined prior to study initiation and updated throughout the study.

Documented approval of the CIP is required from the following groups prior to any study procedures at a study site:

- Medtronic
- CRO (IHF) approvers
- An independent EC (if required)
- Principal Investigator (PI) (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)

Similarly, approval of subsequent revisions to the CIP is required based on the revised contents at each study site from the above mentioned groups prior to implementation of the revised CIP at that site.

13 Steering Committee

The Steering Committee (SC) will be an advisory body to the GOLD AF registry. SC members are responsible for collaboration and guidance on study goals, design and execution and other activities based on expertise and as agreed upon consultancy agreement with the sponsor. Contact information will be provided under the separate cover. This information can be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

14 Final Report and Publications

A final report will be prepared following the last patient has exited the study and the database has been locked.

Medtronic may form the GOLD AF Publication Committee from Steering committee members, study Principal Investigators and Co-Investigators. Medtronic study personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing conclusions and results from the data.

The scientific validity and timing of publications will be evaluated in order to maximize the benefits derived from the publication of the clinical data of the study. Prior to submission of a publication (abstracts and manuscripts), review and approval of the publication will occur by the Medtronic Clinical Study Manager and the manager responsible for oversight of the statistical aspects of the clinical study. Requests for publications utilizing regional data beyond the overall results will be evaluated for scientific validity and the ability of Medtronic to provide resources.

A Publication plan will be established before the first analyses are performed.

Detailed publication policy is described in the Publication Plan, criteria for determining authorship, developing ideas/plans for manuscripts/abstracts, identifying and appointing the manuscript/abstract first author(s) and writer(s), and enforcing timely submission of manuscripts/abstracts.

In order to protect confidential information and/or the interests of Medtronic, all publications (manuscripts and congress presentations) or announcements originating from this study are governed jointly by the Publication Committee and Medtronic. The Publication Committee will maintain an overview of all multi-center publication requests originating from participating physician(s) or Medtronic. It will review and approve them before submission.

Membership in the Publication/Steering Committee does not guarantee authorship.

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (32) will be followed in the reporting of results.

Medtronic personnel can be listed as authors if they meet the ICMJE and target journal authorship criteria.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research, scientific purposes, and educational use.

14.1.1 Investigator Reports

The site is responsible for the preparation (review and signature) and submission of the reports to the sponsor, EC, and regulatory authorities as cited in Table 14-1.

Table 14-1: Investigator Reports per Medtronic Requirements

Report	Submit to	Description
Withdrawal of EC approval	Sponsor and Regulatory Authorities	The investigator must report a withdrawal of approval by the reviewing EC of the investigator's part of the investigation within 5 working days.
Other actions by EC	Sponsor	Any actions taken by the EC that affects any aspect of the study conduct must be submitted to Medtronic as soon as possible.
CIP Reportable Adverse Events (Table 11-2)	Sponsor	Report all reportable adverse events to Medtronic upon awareness.
	EC, Regulatory Authorities (as required)	Report to EC / Regulatory per their requirements/local law.
Geography Specific Reportable Adverse Events	EC, Regulatory Authorities (as required)	Any adverse event that is not collected as part of this clinical study but is required to be reported per local EC or regulatory authority must be submitted per local requirements/law.
Study Deviations	Sponsor	Notice of deviations from the CIP that involves a failure to obtain a patient's consent OR to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. All other deviations should be reported to Medtronic promptly and to EC / Regulatory Authorities per local law.
	EC, Regulatory Authorities	
Progress Report	Sponsor	Provide if required by local law or EC.
	EC	
Final Report	EC, Regulatory Authorities (as required)	This report must be submitted within 6 months of study completion or termination as required per local law or EC.

14.1.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in Table14-2. In addition to the reports listed below, Medtronic shall, upon request of reviewing EC or regulatory authorities, provide accurate, complete and current information about any aspect of the investigation.

Table14-2: Sponsor Reports

Report	Submit to	Description/Constraints
Withdrawal of EC approval	Investigators, Head of Institution, EC, and Regulatory authorities	Investigators, ECs will be notified only if required by local laws or by the EC.

Report	Submit to	Description/Constraints
Withdrawal of Competent Authority (CA) approval	Investigators, Head of Institution, EC, and Regulatory Authorities, upon request	Investigators, EC will be notified only if required by local laws or by the EC.
Progress Reports, if applicable	EC and Regulatory Authorities, upon request	These will be submitted to the EC only if required by the EC.
Final report	Investigators, EC, and Regulatory Authorities, upon request	This will be submitted to the EC only if required by the EC.
Study deviation	Investigators	Site specific study deviations may be submitted to investigators periodically if required.
Adverse Events	Investigators, Regulatory Authorities, EC	Reportable AEs will be provided to regulatory authorities / EC per their requirements. Any negative trends will be reported to participating investigators as appropriate.

15 Transparency

Transparency of study results will be maintained by the following means:

1. A Final Report, describing the results of all objectives and analysis, will be distributed to all PIs, and EC/IRB or CA of participating countries when required by local law
2. Registering and posting the study results on ClinicalTrials.gov based on the posting rules
3. Submitting for publication the primary study results after the study ends

Disclosing financial interests of the co-authors of publications according to the policies set forth by the corresponding journals and conferences.

16 Documentation and Archiving

The investigator is responsible for the retention of the records cited below. All of the below records should be kept in the Investigator Site File (i.e., the study binder provided to the investigator).
The following records must be kept for a period of two years after study closure (or longer as local law or hospital administration requires).

- Subject Identification Log
- Signed and dated PIC/PDRF forms
- All approved versions of PIC/PDRF, and other information provided to the patients and advertisements, including translations
- Signed Delegation Task Log
- Study training records for site staff
- EC/IRB approval documentation, voting list and correspondence with EC/IRB
- Correspondence related to the study
- Reports of AE where applicable
- CIP and any amendments
- PIs Curriculums Vitae
- List of investigation sites
- Regulatory authority notification, correspondence and approval (where required)
- Signed Clinical Trial Agreement between PI/site and sponsor
- Interim or annual reports to EC/IRB, where required
- Final report of the clinical study
- Any other documents required by local requirements.

Medtronic is responsible for the archiving of the documentation for at least three years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required.

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- CIP and any amendment
- Signed Clinical Trial Agreements, current signed and dated Curriculum Vitae of principal investigators, Delegation Task Log
- All signed and dated CRFs submitted and CRF corrections
- All approved informed consent templates, and other information provided to the patients and advertisements, including translations
- Copies of all EC/IRB approval letters and relevant EC/IRB correspondence and EC/IRB voting list/roster
- Names of the institutions in which the clinical study will be conducted
- Regulatory authority notification and approval as required by national legislation
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The CIP study related reports, and revisions
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records required to be stored according to national requirements for medical data

17 References

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18 APPENDICES

APPENDIX 1: Definitions

Table Appendix 1-1: Definitions

Term	Definition
Abnormal kidney function	Presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L.
Abnormal liver function	Chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin .2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase .3 x upper limit normal, etc.).
Alcoholism	Drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days.
Bleeding	Previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anemia, etc.
Dwell time	Time from deployment the first catheter to the LA till removal last catheter from the LA.
Index procedure	First Phased RFA procedure, which is the rational for enrolling the patient into the study.
Labile INR	Unstable/high INRs or poor time in therapeutic range (e.g.<60%).
Long-standing persistent AF	Sustained AF lasting at least 1 year
Paroxysmal AF	Episodes of AF ≥2 recurrent AF episodes that self-terminate, lasting no more than 7 continuous days OR episodes of AF ≤ 48 hours duration terminated with electrical or pharmacologic cardioversion
Peripheral artery disease (PAD)	Atherosclerosis in the peripheral arteries causing narrowing of the arteries. Listed conditions can be considered as PAD: prior revascularization amputation due to PAD angiographic evidence of PAD symptoms of PAD
Permanent AF	Sustained AF lasting > 7 days but no more than 1 year, or sustained AF lasting < 7 days but necessitating pharmacologic or electrical cardioversion.
Repeated procedure	Phased RFA procedure performed as another attempt after unsuccessful index Phased RFA procedure.
Re-ablation procedure	Ablation procedure performed due to recurrence of AF
Unsuccessful procedure	Phased RFA which were evaluated by the operator as unsuccessful (e.g. failure to reach /isolate all PVIs; procedure were terminated due to patient condition/ technical issues)

APPENDIX 2: Summary of changes

Hereby we would like to notify of the protocol update to include the following changes:

The Clinical Investigation Plan has been revised to include the following key changes outlined in details in table Appendix 2 -1: Table of changes in CIP of GOLD AF registry. Above listed changes minor typographical corrections were done.

This protocol notification does not involve any modification related to the patient or to the current management of the study. No procedures or requirements have been added.

Appendix 2 -1: Table of changes in CIP of GOLD AF registry

Location of change	Summary of change and rational
Al pages where version and date are mentioned	Implemented changes compared Version 1.0 06 Feb2016
Contact information and Signatures	**Changes in:** Position name of Ralf Meyer Contact of Project Manager CRO (IHF).
Synopsis – anticipated timelines	Extended for one year anticipated enrolment timelines with a relative extension of study closure and final report **Rationale:** current enrolment rate slower than expected at the study start up
Synopsis – Patient Selection Criteria	Window of sign off informed consent removed from the patient selection criteria and moved to the chapter 7.2 "data collection process; enrollments" on page 28. **Rationale:** window of PIC/PDRF sign off is not an important criteria of patient selection and it rather represents study procedures This change has been made throughout the document wherever the inclusion criteria is referenced.
Synopsis - Sites	**Changed from:** Approximately 50 centers across Europe and Israel **To:** Approximately 38 centers across Europe, Israel and South Korea. Additional sites and regions might be considered and added subsequently **Rationale:** Less than anticipated, sites confirmed participation South Korean sites were added. This change has been made throughout the document wherever the inclusion criteria is referenced.
Synopsis - Data Collection	Deviation form was added Deviation eCRF also will be implemented in eCRF **Rationale:** In CIP, V1 paper Deviation form was applied to record study deviations. To unify the process Deviation form was programmed in the database. This change has been made throughout the document wherever the inclusion criteria is referenced.
Synopsis - Data Collection	**Changed from:** Site Questionnaire (one time before the center enrollments) **To:** Site Questionnaire (one time before the center enrollments and updates if new operators join the registry). **Rationale:** Site Questionnaire needs to be updates if new operators join the registry. The operators can change in one hospital over the time and it is important to record experience of operators performing procedures. The process were applied the same way under the CIP V1, but was not clarified in CIP.
3.4 Methodology	**Added:** Subjects can sign PIC/PDRF 14 days prior to the scheduled Phased RFA procedure to have sufficient time to consider the participation in the registry. **Rationale:** Extended window of sign off PIC/PDRF until two weeks before the hospitalization for the index Phased RFA procedure based on feedback from investigators. This change has been made throughout the document wherever the inclusion criteria is referenced.

3.5 Quality of Life	**Added:** The validated languages cover the following: French, German, Italian, Spanish (Spain), Polish and Dutch, Korean. The AFEQT questionnaire will be applied to all patients, either in the linguistically validated country-specific version or, if a country-specific validated version does not exist, in the not validated version translated into the local language of the respective patients according to local requirements and regulations. To avoid possible confounders, all analyses regarding the AFEQT questionnaire will be performed for the overall sample and stratified by validated vs not validated version. This also applies to the mode of questionnaire administration: In general, the AFEQT questionnaire will be filled in by the patient himself. However, in some sites the AFEQT questionnaire will be administered by telephone interview. To avoid possible confounders, all analyses regarding the AFEQT questionnaire will be performed for the overall sample and stratified by self-administered vs administered by telephone interview. **Added:** It is recommended that the questionnaire is completed at baseline and at 12 months FU. At baseline AFEQT can be completed starting from 14 days prior to the hospitalization for the index Phased RFA procedure if patients consent their participation in the registry. **Rationale:** to clarify the utilization of non-validated languages, as well as the utilization of questionnaire in case or remote follow up.
3.6 Participating Sites	**Changed from:** is planned to include approximately 50 sites in 10 countries (Germany, Netherlands, United Kingdom, Belgium, Italy, Spain, Switzerland, Israel, Poland, and France). **To:** Approximately 38 sites in 13 countries (Germany, Netherlands, United Kingdom, Hungary, Italy, Spain, Switzerland, Israel, Poland, Portugal, France, Greece and South Korea) are anticipated to take part in the registry. **Rationale:** roiling changes in number and list of participating sites and was defined in CIP V1.
Site activation	**Added:** In order to obtain database access details, the database User Account Request form should be signed by personnel delegated to work with eCRF. A scanned copy needs to be sent to the sponsor or designee. The process was applied the same way under the CIP V1, but was not clarified in CIP.
4.4 Statistical methods	**Added:** More detailed information about endpoint definitions, analysis method, limitations, and measurements to be applied. Rational: in CIP V1 statistical methods were described vaguely. Due to Statistical Analysis Plan finalization methods can be described more precisely.
4.4 Statistical methods	**Changed from:** Re-ablations for left AfI **To:** Ablations for left AfI or left AT. **Rationale:** Change made based on feedback of SCMs and site PIs. After AF ablation, different types of left AT are possible, including left AfI. AT represents a more comprehensive definition.
5.1 Premature termination	**Added:** Premature termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single site. **Rationale:** Added definition of premature termination and suspension.
5.1 Premature termination or suspension	**Added** possible reason for study termination/suspension "Slow enrollment rate, which does not allow to reach the anticipated sample size"
5.1 Premature Termination or suspension	**Added:** 5.1.1 describing procedure for termination or suspension

6.3 Ethical Review and Regulatory Consideration	**Added:** The GOLD AF Registry was designed to reflect the GCP principles, including the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. **Added:** The study will be conducted according to national and local laws, regulations, standards, and requirements of the countries / geographies where the study is being conducted and the Clinical Investigation Plan (CIP), Clinical Trial Agreement (CTA) at each participating site. **Rationale:** These principals were applied with a CIP V1, but were not described.
7.1 Data Collection Procedure	**Added:** The GOLD AF database is reachable at the following link http://studien.herzinfarktforschung.de/goldaf. Case report forms for this study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data system after the site has fulfilled all requirements for database access. **Rationale:** These procedures were applied with a CIP V1, but were not described in CIP.
7.1 Data Collection Procedure	**Changed from:** At the end of the study, the data will be frozen and retained for at least 10 years by the sponsor. **To:** At the end of the study, the data will be frozen and retained and will be retained per sponsor policy. **Rationale:** requirements for the data retention can change over time.
7.2 Data collection process, Procedure visit	**Added:** If patient has re-do procedures with some other technology than Phased RFA, Procedure CRF is not required; whilst, information about technology which was used for re-ablation is to be collected in eCRF "General FU" During the Phased RFA , the investigator may require use of other commercially available devices for other ablations such as Afl /AT or other AF triggers. The use of other devices will be at the investigator's discretion and use will be documented on the eCRF. Hospital discharge needs to be completed when the patient is discharged, and this data is to be collected as part of the procedure visit. Information about date of discharge, reportable adverse events since the procedure and recommended medication information is to be collected. Post-ablation drug regimen is determined at clinical discretion of the treating investigator. **Rationale:** These approach were applied with a CIP V1, but were not described in CIP.
7.2 Data collection process	**Added:** information about study exit
7.2 Data collection process	**Added:** Table 18-2: Follow Up Visit Windows. **Rationale:** to mitigate variations in clinical care practices for unscheduled hospital visits for Statistical Analysis Plan.
7.5 Monitoring	**Deleted:** Information about remote monitoring. **Rationale**: remote monitoring (e.g. calls or web ex performed from CRO) to the sites were not accepted by some sites as convenient tool of follow up due to the language barrier. Instead sites are called or visited by Medtronic country clinical representative if support is required. Onsite monitoring visits will be performed according to the Monitoring Plan.

7.3 Source documents	**Added:** Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, QoL questionnaires must be created and maintained by the investigational site team. The investigator will clearly mark clinical record to indicate that the subject is enrolled in this study. **Added:** The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. **Rationale:** These procedures were applied with a CIP V1, but were not described in CIP.
7.4 Deviations from the CIP	**Replaced:** Chapter name renamed on Study Deviations **Rationale:** Through the registry not only CIP related deviations can take place
7.4 Study Deviations	**Added:** Examples of the study deviations.
7.4 Study Deviations	**Added:** Study deviations need to be documented in the eCRF "deviation Form" which contains the following data: Administrative information (e.g. Case No for patient identification, site ID; date of Deviation) Deviation description Reason for Deviation Action taken The eCRF "Deviation Form" can be completed by the site personnel or by the sponsor of designee in cooperation with the site personal and has to be signed by authorized site person. **Rationale:** to see changes about adding eCRF "Deviation Form" which earlier were used in hand writing.
11 Adverse events	**Added:** Table 11-2. was added with ISO definitions of the following adverse events: Device deficiency, Adverse Device Effect, Serious Adverse Device Effect, Unanticipated Serious Adverse Device Effect. **Rationale:** Study required (reportable) adverse events stays unchanged, no changes for the site or for the patient. AEAC can adjudicate relatedness of the AEs as not related to the procedure/system or classified according to the table 11.2 using the aforementioned definitions.
11 Adverse events	**Added:** If AE is not resolved at the moment of completeness, AE update needs to be completed upon AE resolution. All efforts should be applied to follow unresolved adverse events until they has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first. **Rationale:** This condition were applied on CRF with a CIP V1, but were not described in CIP.
11 Adverse events	**Added:** Collection of information about patient death in 11. 1.1. Patient Death **Rationale:** The same approach was applied in eCRF under the CIP V1
12 Legal requirements	**Changed from:** This registry fulfils the requirements of the Directive 2001/83 EC, title IX and Volume 9A of The Rules Governing Medicinal Products in the EC, the Declaration of Helsinki 2013 (30) and will be conducted in accordance with the respective SOPs of the CRO. **To:** This registry fulfils the requirements of the Directive 2001/83 EC, title IX and Volume 9A of The Rules Governing Medicinal Products in the EC, the Declaration of Helsinki 2013 and later versions throughout the study (30) and will be conducted in accordance with the respective SOPs of Medtronic and CRO (IHF). **Rationale:** Added that Medtronic SOPs to be used in addition to CRO (IHF) SOPs. Added that later versions of Declaration of Helsinki will be applicable in case of update.

13 Steering committee	**Deleted:** List or Steering Committee names. **Rational:** List of SC members can change through the study duration and therefore will be provided under a separate cover
14 Final report and publications	**Added:** A final report will be prepared following the last patient has exited the study and the database has been locked. **Added:** Membership in the Publication/Steering Committee does not guarantee authorship. **Added:** Medtronic personnel can be listed as authors if they meet the ICMJE and target journal authorship criteria. **Rationale:** Since the As far as Publication Plan has been were finalized these details have been were added to CIP.
14.1.1 Investigator Reports	**Added:** table summarizing possibly required investigator reports **Rationale:** Provide transparency
14.1.2 Sponsor reports	**Added:** table summarizing possibly required sponsor reports **Rationale:** Provide transparency