GOLD AF

Registry

Statistical Analysis Plan

Version 1.1

19.12.2018

Sponsor:
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CRO:
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Signature Page

We, the undersigned, have carefully read this Statistical Analysis Plan and agree that it contains all necessary information required for statistical analyses of the GOLD AF registry:

Signature	***Date***
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Version History

Version	Date	Author	Changes
DRAFT Versions	13.05.2015	Dr. Alexandra Bernhardt Martin Horack	Initial development
Version 1.0	31.08.2017	Martin Horack	Update, minor changes
Version 1.1	21.12.2018	Christiane Lober Martin Horack	definition changes in Analysis sets, adapt to updated FU windows and handling follow-ups, add analysis specifications and details in endpoint relevant calculations, add subgroup analysis and comparisons (appendix), adding EFAS (analysis set) Updates according to Quality Meeting of 25th of October 2018

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Abbreviations

12MFU	12 months follow-up
ACE inhibitors	Angiotensin-Converting
ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life (Questionnaire)
Afl	Atrial Flutter
ASA	AcetylSalicylic Acid
AT II antagonist	Angiotensin Receptor II Antagonist
AV-Block	AtrioVentricular Block
CABG	Coronary Artery Bypass Graft
CFAE	Complex Fractionated Atrial Electrograms
cGy	CentiGray
CHA2DS2-VASc	Score for Stroke Risk Components: cardiac failure,hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)
CI	Confidence Interval
CIP	Clinical Investigational Plan
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organisation
CRT	Cardiac Resynchronization Therapy
CT	Computed Tomography
CV	Cardio Version
CVD	Cardiovascular Disease
DAP	Dose Area Product
dd.mm.yyyy	Date with Day.Months.Year
EBogen	Electronic Data Capture System of the Institut für Herzinfarktforschung
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGM	Electrogram
EHRA	European Heart Rhythm Association
EP	Electrophysiology
FU/GFU	Follow-up/General Follow-up
GmbH	Gesellschaft mit beschränkter Haftung (limited liability company)
HAS-BLED	Score for Major Bleeding Risk Components: hypertension, abnormal renal/liver function (1point each), stroke, bleeding history or predisposition, labile INR, elderly (>65), Drugs/alcohol concomitantly (1 point each)
HF	Heart Failure
hh:mm	Time with Hours.Minutes
ICD	Implantable Cardioverter-Defibrillator
ICM	Implantable Cardio Monitor
IHF	IHF GmbH - Institut für Herzinfarktforschung, Ludwigshafen

ILR	Implantable Loop Recorder
INR	International Normalized Ratio
IPG	Implantable Pulse Generator
IVC	Inferior Vena Cava
kg	Kilogram
LA	Left Atrium
LAAO	Left Atrial Appendage Occluder
LCPV	Left Common Pulmonary Vein
LIPV	Left Inferior Pulmonary Vein
LMWH	Low-Molecular-Weight Heparin
LSPV	Left Superior Pulmonary Vein
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MAAC	Multi-Array Ablation Catheter
MASC	Multi-Array Septal Catheter
MDT	Medtronic
mGy*cm^2	MilliGray Square Centimeters
MI	Myocardial Infarction
min	Minute
ml	Milliliter
mm	Millimeters
mmHg	Millimeters of Mercury
MRI	Magnet Resonance Imaging
NA	Not Applicable
NIS	Non-interventional Study
no.	Number
NOAC	Novel Oral Anticoagulant
NSAID	NonSteroidal Anti-Inflammatory Drugs
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
Op	Operator
PAF	Paroxysmal Atrial Fibrillation
PCI	Percutaneous Coronary Intervention
PDRF	Patient Data Release Form
PIC	Patient Informed Consent
PV	Pulmonary Vein
PVAC	Pulmonary Vein Ablation Catheter
PVI	Pulmonary Vein Isolation
Q1	Lower Quartile
Q3	Upper Quartile
QoL	Quality of Life
RA	Right Atrium
RF	Radiofrequency
RFA	Radiofrequency Ablation
RIPV	Right Inferior Pulmonary Vein
RMPV	Right Middle Pulmonary Vein
RSPV	Right Superior Pulmonary Vein
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
sec	Second
SVC	Superior Vena Cava
TEE	Trans-Esophageal Echocardiography
TIA	Trans-Ischaemic Attack
TTE	Trans-Thoracic Echocardiogram
VF	Ventricular Fibrillation
VKA	Vitamin K Antagonist
VT	Ventricular Tachycardia

1 Introduction

1.1 General Information

The intention of this Statistical Analysis Plan is to specify procedures regarding all planned statistical analyses within the framework of the GOLD AF registry performed by the IHF GmbH - Institut für Herzinfarktforschung, Ludwigshafen. The overall objective of the SAP is to ensure the credibility of the study data by describing the statistical methodology to be used to evaluate the baseline and follow-up data of the GOLD AF registry.

The initial version of the Statistical Analysis Plan will be completed before first database lock. However, any of the following points may become subject to alterations during the course of the study. Significant changes to statistical analyses shall be discussed with the Statistical Analysis Plan approvers prior to their implementation. All parties affected by changes are to be informed by the author of the changes.

If necessary, selected tasks may be delegated to authorised and adequately qualified designees by the assigned personnel without the need to update the Statistical Analysis Plan. However, the responsibilities remain with the personnel assigned in the Statistical Analysis Plan.

By the time of database lock, the Sponsor Project Responsible shall receive the final version of the Statistical Analysis Plan.

This is a non-interventional registry. The statistical analysis will be performed on an exploratory and descriptive basis and there are no initial hypotheses to be tested.

This Statistical Analysis Plan has been written based on the following documents for this prospective non-interventional registry GOLD AF:

- Clinical Investigational Plan (Version 1.0 dated 06-Feb-2015)
- Clinical Investigational Plan (Version 2.0 dated 09-Sept-2016)
- Case Report Form (Version 1.3 dated 30-APR-2015)
- Case Report Form (Version 1.4 dated 13-Jan-2017)
- Annotated Case Report Form (Version 1.3) – Appendix E
- Annotated Case Report Form (Version 1.4) – Appendix E
- Data Management Plan (V1.2 dated 05-Jul-2016)
- Online Data Validation Plan (V1.0 dated 21-SEP-2015)

1.2 Statistical Site

The statistical analysis of this registry will be performed by the following Contract Research Organisation (CRO):

IHF GmbH – Institut für Herzinfarktforschung
Bremserstr. 79, 67063 Ludwigshafen/Rhine, Germany
Phone: +49 621 59577 222
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The responsible CRO statistician is:

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Email: horack@ihf.de

1.3 Software

Statistical analysis will be carried out using SAS®, release 9.3 or higher (SAS Institute Inc., Cary, NC, USA) on a Microsoft® Windows® 7 or a Microsoft® Windows® 10 Enterprise platform.

2 Objectives of the Non-interventional Study

2.1 Main Objective

The primary objective of this study is to assess the Phased RF ablation success rate after 12 month follow-up in patients with AF who are scheduled for Phased RFA.

2.2 Secondary Objectives

Ancillary objectives of this study are as follows:

- 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 Design

3.1 Design

The GOLD RF registry is a postmarket release (PMR), prospective, observational, multicentre, clinical study in consecutive subjects with atrial fibrillation treated with the phased RFA technology (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 valid Instructions for Use (IFU) as well as according to medical society guidelines and the clinic's internal directives. Medication-based therapy should also meet medical society guidelines or the clinic's internal directives, respectively.

40 sites in 14 countries (Germany, Netherlands, United Kingdom, Hungary, Italy, Spain, Switzerland, Israel, Poland, Portugal, France, Greece, Georgia and South Korea) are anticipated to take part in the registry to get documentation on at least 800-1000 patients (for more details regarding sample size consideration, see Section 3.3 in the SAP). Eligible for participation are study sites and hospital-based physicians treating AF subjects with phased RFA technology. The enrolment period is estimated to be 24 months. The individual observation period per patient is up to 12 (+2) months: Based on the observational plan, it is planned that the baseline visit is conducted by the investigators. All follow-up visits in the registry are unscheduled. They will be conducted in accordance with "routine clinical practice" in the participating medical centres: Between the procedure date and the following 12MFU period, any general FU will be captured. General FUs might occur due to site specific visit schedule, related to AF re-occurrence (re-ablation, AF symptoms, CV etc.) or due to patient visits at the site because of AE related symptoms. At 12MFU window, the patient will either be followed up in the medical centre or by phone.

3.2 Flow Chart

Data Collection*	Baseline	Procedure first documented, additional	General Visit/ FU	12 months FU in hospital	12 months FU by phone
Enrolment (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
Adverse events (AEs)	- Whenever occur -				

*= prior to first patient enrolment 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.

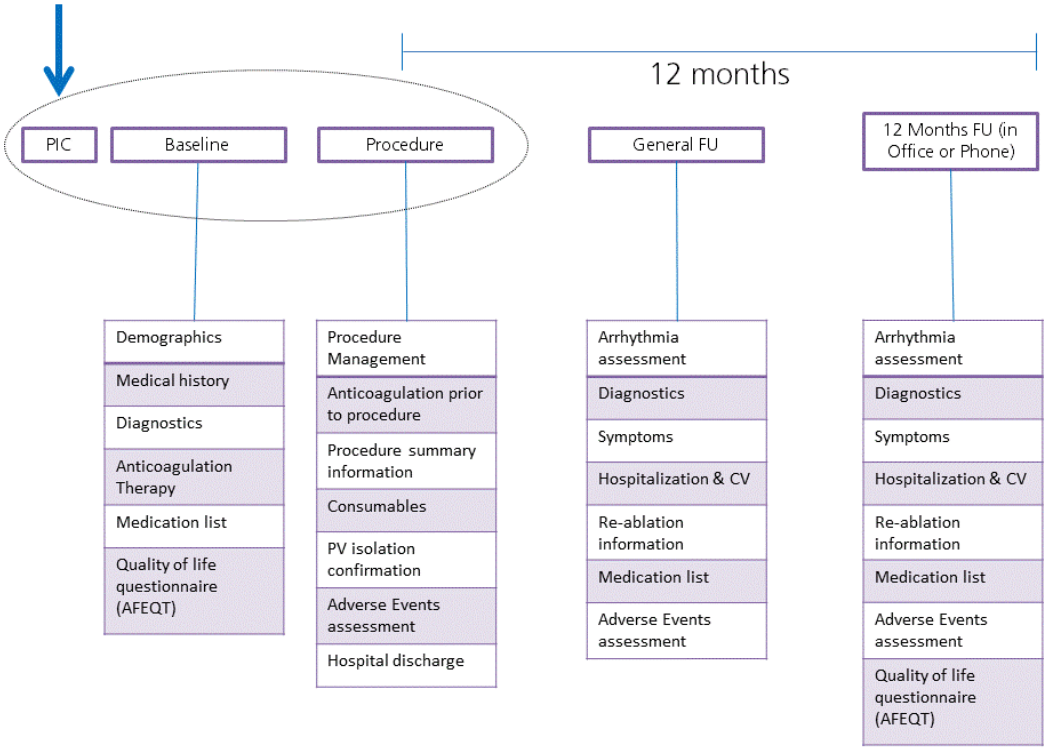

Figure 1: Study design – flow chart.

3.3 Sample Size Determination

The sample size calculation is based on the main objective to document real life mid-term efficacy of patients with atrial fibrillation who were scheduled for phased RF ablation. Efficacy is in this case assumed as the proportion of redo ablations 12 months after treatment.

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

Table 1: Cross 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% 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 re-ablation 12 months after treatment of 20%, a sample size of 800 will allow the study to estimate the prevalence with a given precision of ± 3.8% [range of 95%-CI: 7.6%]. This size guarantees sufficient information to estimate the prevalence in smaller subgroups (e.g. subgroup with a prevalence of 25% with a precision of ± 6.6% [range of 95%-CI: 13.3%]).

A drop-out rate of 25% is assumed (i.e. an estimated drop-out of about 200 patients). Thus, it is planned to enrol a total number of patients of at least 800 - 1000.

4 Analysis Sets

Analysis sets will be predefined and selected for each analysis to be carried out, based on the scope of the analysis. The Appendix B will give an overview about analysis tables, study objectives and analysis sets. Analysis sets might be used for further analysis. The following analysis sets will applied:

4.1 All-Documented Patient Set

The *All-Documented Patient Set* (APS) consists of all patients with signed patient informed consent (PIC) and complete date of PIC who have any additional eCRF documentation, i.e. with non-empty eCRF information for at least one further collection point. In case of a missing PIC/PDRF or an incomplete date of PIC/PDRF, the entry for that patient in the database is only formally created and no further information (at least on further eCRF pages) can be added.

In case that a given PIC/PDRF is drawn back during the course of the registry (i.e. PIC/PDRF is set from "yes" to "no" during the visit), entries that have already been made are not deleted. These entries should be set to missing in the analysis data sets.

If a patient exits from the study, data collected prior to the study withdrawal will be included in the analysis in compliance with PIC/PDRF unless the patient object and ask for deletion of the data or when required by local regulations.

The APS will be used for total registry analysis (interim ,final and post-hoc analysis).

4.2 Baseline Analysis Set

The *Baseline Analysis Set* (BAS) consists of all patients of the APS and patients:

- where baseline signature has been taken (signed eCRF)
- with AF who are scheduled for Phased RFA
- that meet all remaining eligibility criteria
- provide any further documentation at baseline
- a phased RFA procedure was started - procedure form was fulfilled at least: date of the procedure, PVAC GOLD catheter used (opened), number of PV applications > 0
- patient did not exit the study prematurely for the reason: Patient were enrolled, but Phased RFA procedure was not started

According to the Appendix B, the BAS will be used for the interim and final analysis as well as for post-hoc analysis. The final analysis includes the additional objective (SAP chapter 8.2) and ancillary objectives (SAP chapter 8.3), where the BAS will be applied.

4.3 Full Analysis Set

The *Full Analysis Set* (FAS) consists of all patients of the BAS and thereof patients with a valid 12MFU form of 12 months visit or 12 months telephone interview. The rules for valid 12MFU form are described in the chapter 7.2.3.

A documented 12MFU form includes at least:

- Date of the visit/FU and
- Vital status and
- Signed eCRF 12MFU visit or 12MFU by phone form

The FAS will be used to analyse the main objective (SAP chapter 8.1), additional objective (SAP chapter 8.2) and ancillary objectives (SAP chapter 8.3). The FAS will be analysed at the end of this study.

4.4 Extended Full Analysis Set

The *Extended Full Analysis Set* (EFAS) consists of all patients of the FAS and thereof patients without documented AF re-ablation (each ablation technology i.e. additional GOLD-AF procedure) until the 12MFU (<351d after the first documented procedure). Also, only patients with a successful first documented procedure (by PVI confirmation) will be member of the EFAS. This population will be used to evaluate the effect of the first documented procedure, in a clearer way.

5 For analysis, the EFAS will be used in the same way as the FAS.Protocol Violations

In this registry, the analysis is limited to patients with signed patient informed consent and complete date of patient informed consent (otherwise no further entry in the eCRF was possible) who are scheduled for Phased RFA for AF catheter ablation treatment. Furthermore, the patients have to fulfil the eligibility criteria of an age ≥18 years as well as a signed PIC/PDRF which allows the analysis of collected personal data during the participation in the registry (up to 14 months after the initial Phased RFA procedure). CRF forms documented 14 months after procedure (440 days) will be ignored for analysis.

In this registry it is not distinguished between a broader full analysis set and a more compliant per-protocol set that excludes all major violators. Therefore, the definition of major violators is not applicable.

6 Target Variables

6.1 Study Population

Data from all patients who are enrolled in the study (patients who meet the eligibility criteria and signed the PIC/PDRF) will be included in the analysis. If a patient exits from the study, data collected prior to the study withdrawal can be included in the analysis in compliance with PIC/PDRF unless patient requests deletion of the personal data when exit the study in compliance with local regulations.
The following parameters will be used to characterise the study population and to give an overview on the documented visits:

- Overview about patient status
  - number of patients in the All-Documented Patients Set (APS),
  - number of patients in Baseline Analysis Set (BAS),
  - number of patients in Full Analysis Set (FAS)
  - number of patients in Extended Full Analysis Set (EFAS)
- Overview about reasons for being excluded from the different analysis sets
  - Criteria for the BAS
  - Criteria for the FAS
- Number of documented patients per site (BAS)
- Number of documented patients per visit and visit period (FAS)
- Number of documented visits per patient (FAS)
- Number of documented patients by visit pattern (FAS)

A patient is defined as "documented" at a respective visit, if the FU form has a date of the visit and it is non-empty (at least one further entry) for that visit.

6.2 Analysis Variables

All appropriate information of the following eCRF sections will be used to characterise the study populations (see Appendix D: Annotated Case Report Form V1.3 and V1.4). Data will be displayed based on their entity type (SAP chapter 7.2).

- Demographics and other Baseline Characteristics, Procedure Documentation
- Follow-up Documentation: General FU
- Follow-up Documentation: 12 Months FU
- Follow-up Documentation: 12MFUby Phone
- Adverse Event Form (SUO form)
- Study Exit Form
- Quality of Life Questionnaires

6.3 Quality of Life Questionnaires

In this registry, QoL will be assessed with the *Atrial Fibrillation Effect on Quality of Life* (AFEQT) questionnaire. It is a standardized, disease-specific, reliable and responsive measure of health-related QoL in patients with atrial fibrillation. The AFEQT is a self-reported

questionnaire with responses on a 7-point Likert scale. The 20-item instrument is divided into three domains (a 4-item Symptom score, an 8-item Daily Activities score, a 6-item Treatment Concerns score) plus two Treatment Satisfaction questions. The domains Symptoms, Daily Activities and Treatment can be aggregated into an overall score.

For all questionnaires, the frequencies of the given answers are presented by country and overall. If - based on the answers – scores are constructed these are presented, too.

The AFEQT questionnaire consists of 3 functional subscales (Symptoms [4 items], Daily Activities [8 items], Treatment Concern [6 items]) that are part of the overall AFEQT score. The 2 questions on Treatment Satisfaction are computed as its own subscale similarly to the overall score.

- Symptoms [*not at all bother OR I did not have this symptom; hardly bothered; a little bothered; moderately bothered; quite a bit bothered; very bothered; extremely bothered*]:
  - Palpitations: Heart fluttering, skipping or racing
  - Irregular heartbeats
  - Pause in heart activity
  - Light-headedness or dizziness
- Daily Activities:
  - Ability to have recreational pastimes, sports, and hobbies [*not at all limited; hardly limited; a little limited; moderately limited; quite a bit limited; very limited; extremely limited*]
  - Ability to have a relationship and do things with friends and family [*not at all limited; hardly limited; a little limited; moderately limited; quite a bit limited; very limited; extremely limited*]
  - Doing any activity because you felt tired, fatigued, or low on energy [*no difficulty at all; hardly any difficulty; a little difficulty; moderately difficulty; quite a bit of difficulty; a lot of difficulty; extreme difficulty*]
  - Doing physical activity because of shortness of breath [*no difficulty at all; hardly any difficulty; a little difficulty; moderately difficulty; quite a bit of difficulty; a lot of difficulty; extreme difficulty*]
  - Exercising [*no difficulty at all; hardly any difficulty; a little difficulty; moderately difficulty; quite a bit of difficulty; a lot of difficulty; extreme difficulty*]
  - Walking briskly [*no difficulty at all; hardly any difficulty; a little difficulty; moderately difficulty; quite a bit of difficulty; a lot of difficulty; extreme difficulty*]
  - Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping [*no difficulty at all; hardly any difficulty; a little difficulty; moderately difficulty; quite a bit of difficulty; a lot of difficulty; extreme difficulty*]
  - Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball [*no difficulty at all; hardly any difficulty; a little difficulty; moderately difficulty; quite a bit of difficulty; a lot of difficulty; extreme difficulty*]
- Treatment Concern [*not at all bother; hardly bothered; a little bothered; moderately bothered; quite a bit bothered; very bothered; extremely bothered*]:

    - Feeling worried or anxious that your atrial fibrillation can start anytime
    - Feeling worried that atrial fibrillation may worsen other medical conditions in the long run
    - Worrying about the treatment side effects from medication
    - Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemaker therapy
    - Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising
    - Worrying or feeling anxious that your treatment interferes with your daily activities
- Treatment Satisfaction [*extremely satisfied; very satisfied; somewhat satisfied; mixed with satisfied and dissatisfied; somewhat dissatisfied; very dissatisfied; extremely dissatisfied*]:
    - How well your current treatment controls your atrial fibrillation
    - The extent to which treatment has relieved your symptoms of atrial fibrillation

For the scoring of the AFEQT, see chapter 7.4.3 in the SAP.

6.3.1 Ensure AFEQT data quality for analysis

The following test procedure is planned to admit the use of the AFEQT questionnaire in the GOLD AF registry. Prior analysis, possible effects are needed to discover regarding the following issues:

a. the use of AFEQT data from not validated language versions
b. the use of AFEQT data that were not self-administered by the patients, but documented by sites in telephone interviews.

Step 1: Validated and not validated AFEQT language versions

The following language versions used in this registry are validated: French, German, Italian, Spanish, Polish, Dutch, English and Korean. The following language versions used in this registry are not validated: Georgian, Greek, Hungarian, Hebrew, Arabic, Russian and Portuguese.

To evaluate whether validated and not validated language versions differ from each other, baseline AFEQT scores will be compared between both groups, i.e. evaluation of homogeneity of both distributions (Wilcoxon-Mann-Whitney test, two tailed, $p<0.05$). It will be assumed, that both patient sets are equal in their medical history. Further predictors or confounders will not be considered. If the difference proves to be statistically significant, data derived from not validated language versions will be excluded from further analyses. Otherwise, step 2 will be evaluated.

Step 2: Self-administered and interview data

The AFEQT was developed and validated as a self-administered questionnaire. However, a currently unknown number of AFEQT questionnaires (i.e. especially those documented during hospital visits) will be collected by the sites and at the 12 months follow-up by phone AFEQT questionnaires will be documented during telephone interviews.

To evaluate whether self-administered and interview data differ from each other, data from both groups (self-administered vs. interview) will be compared (i.e. evaluation of homogeneity of distributions, Wilcoxon-Mann-Whitney test, two tailed, $p<0.05$). If the difference proves to be statistically significant, data from both groups will not be merged, but analysed separately.

Structure and consequences of planned tests:

Scenario 1: Statistically significant difference between validated and not validated language versions

→ Exclusion of data from not validated language version from all further analyses

Scenario 2: No statistically significant difference between validated and not validated language versions

→ Merging and release AFEQT data for step 2

Scenario 3: Statistically significant difference between self-administered and interview data, but no statistically significant difference between validated and not validated language versions

→ Merging of AFEQT data from validated and not validated language versions and separate analyses of data from both groups (self-administered vs. interview) regarding all further analyses

Scenario 4: No statistically significant difference between self-administered and interview data and no statistically significant difference between validated and not validated language versions

→ Merging of AFEQT data from validated and not validated language versions and merging of data from both groups regarding all further analyses

7 Data Handling

This chapter contains instructions for data handling which are generally decisive for derived variable calculations and data presentation.

The basis for time calculations will be the first documented procedure (SAP chapter 7.4.1).

In order to assess the effects of patients lost to follow-up, percentages of dropouts and reason for loss to follow-up 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 (SAP chapter 8.6). Patients who withdrawal the PIC/PDRF will be handled according to SAP chapter 6.1.

7.1 Definitions

Pre-post differences

Pre-post differences in absolute values (also called absolute changes) will always be calculated as post-baseline value minus baseline value.

Relative pre-post differences

Relative pre-post differences (also called percent changes) will always be calculated as 100% (post-baseline value minus baseline value) / baseline value.

Pre-post differences will be calculated for the following variables (other can be proposed retrospectively):

Table 2: Variables for pre-post differences

Variables	Pre- value	Post- value	Derived variables
Antiarrhythmic medication Anticoagulation medication Antiplatelets Other cardiovascular medication	Discharge	12MFU visit/ 12MFU by phone	Number of patients • Never on • Newly on • Continued • Discontinued
AFEQT-Score	Baseline	12MFU/ 12MFU by phone	Absolute change in AFEQT score
AF burden	Baseline	12MFU visit/ 12MFU by phone	Absolute change in AF burden [%]
EHRA AF symptoms classification	Baseline	12MFU visit/ 12MFU by phone	

7.2 Handling data entity types

The CDISC data export is arranged according to the tables in the eCRF (see Data Management Plan). These tables contain data of entities, whose definitions only partially correspond to the entity types processed in statistical analysis. The aim of the analysis is to show the data at patient level.

The following entity types can be used for statistical analysis:

1. Patient
2. Procedure
3. Follow-up
4. Adverse Event

7.2.1 Patient data

Data will be analysed showing data on patients level according the eCRF segments enrolment, demographics, medical history, concomitant diseases, diagnostics, medication, hospital discharge, quality of life (AFEQT) and study exit.

7.2.2 Procedural data

Procedure data will be displayed separately according to their chronology. Additional procedures will be shown individually including all procedure details, such as for the first documented procedure. The first documented procedure is the basis for main objective calculations (SAP chapter 8.1). Discharge belonging to procedure: Hospital discharge after an additional procedure. For patients with several procedures, there may be several discharge events, too. All events will be processed and analysed, just as the medications associated with the procedure.

7.2.3 Follow-up data

Only unique 12MFU form per patient will be used for analysis. If a General Follow-up visit meets the time window of the 12MFU visits (>351d after procedure), manually data review and selection will be performed. Any FU forms older than 440 days after procedure will not be used for analysis (protocol deviation). For patients with contradictory information in the eCRF the following rules are applied:

1. 12 month FU (by phone or visit) is preferred to GFU.
2. Events are always kept, even if GFUs are discarded.

The decision on patient level is given in Appendix F.

12MFU visit and 12MFU by phone results will be analysed combined, where variables were recorded in a similar manner (demographics, symptoms, hospitalization, medication). Not combinable information will be shown separately.

General FU (GFU) data will be assigned to the respective time period after first documented procedure:

- 0 to 3 months (1 day =< time between procedure and GFU <= 90 days)
- 3 to 6 months (90 days < time between procedure and GFU <= 180 days)
- 6 to 9 months (180 days < time between procedure and GFU <= 270 days)
- 9 to 12 months (270 days < time between procedure and GFU <= 351 days)

Multiple GFU per patient within one time period will be shown separately in chronological order (i.e. all first GFUs in one time period, all second GFUs in one time period and so on) as descriptive tables.

Number of GFUs per time period and time (days) until GFU during the time period (for each visit per time period) will be shown. Event rates for clinical events (history of AF, re-ablations and hospitalizations) will be calculated for 3, 6 and 9 months after discharge exactly using appropriate statistical methods.

Predefined time windows for GFU from CIP Version 2.0, Table 7.2 will not be applied.

7.2.4 Adverse Event data

Adverse event data (from AE form) will be listed, ordered and reported by seriousness and relatedness to the procedure. Further adverse event analysis are described in the additional objective of this study (SAP chapter 8 and 8.2). For Adverse event analysis only AEAC adjudicated (SUO form) events will be analysed.

7.3 Categorisations

Variable categorisations will be done and displayed for all variables created for subgroup definitions (number of patients treated with PVAC GOLD solely). Following variable categorisations will be also displayed:

- Age by categorisation 1 [years]: <65, 65-74, ≥75
- Age by categorisation 2 [years]: <65, 65-75, >75, 75-80, >80
- Weight [kg]: ≤60, >60
- Body Mass Index [kg/m²]: <18.5, 18.5 to <25, 25 to <30, ≥30 (including WHO obesity classes I-III)
- Number of drinks/day > 10
- HAS-BLED: low, medium, high risk (defined at SAP chapter 7.4.2.1)
- CHA2DS2-VASc: low, medium, high risk (defined at SAP chapter 7.4.2.2)
- Previous ablation (none, 1, ≥ 2)
- Previous surgery for AF (none, 1, ≥ 2)
- Hospitalizations due to AF (none, 1, ≥ 2)
- INR before ablation (INR≤1, 0.85<INR<1.27, INR≥1)

All other categories will be determined based on the distribution of the respective baseline data. Additional categorisations can be added, if necessary.

7.4 Transformation of Data

7.4.1 (Re-)Calculation of derived variables

Body Mass Index [kg/m2]
ROUND (body weight [kg] / (body height [cm] / 100) ^2), .01)

Time to event

For the time to event analysis, the time until the occurrence of an event is presented in days [d] and calculated as follows:

Date of event occurrence – date of first documented procedure

Length of stay in rehabilitation [days]
ROUND((Date of discharge - Date of referral),1)

DAPT [dichotomous]
Dual antiplatelet therapy: Combination of Aspirin and an $P2Y_{12}$ inhibitor (Clopidogrel, Prasugrel or Ticagrelor).

Procedure Timing

- General time of the procedure = defined and calculated by eCRF
- Time in between vessel access = time of last catheter removal – first vessel access
- Lab occupancy time = Time patient left the Catheter Lab - Time patient delivered to the Catheter Lab
- PVAC ablation time = Time of last PVAC ablation - Time of first PVAC ablation
- MAAC duration = Time of last MAAC ablation - Time of first MAAC ablation
- MASC duration = Time of last MASC ablation - Time of first MASC ablation

7.4.2 Risk scores

7.4.2.1 HAS-BLED Score

The HAS-BLED Score is based on nine variables which contribute (if fulfilled) to the score by each point:

Risk Factor / Variable	Points
Hypertension*	1
Abnormal	
renal function	1
liver function	1
Stroke/TIA	1
Bleeding	1
Labile INR	1
Elderly (> 65)	1
Drugs (antiplatelets or NSAID)	1
alcohol abuse**	1

* Hypertension is defined as present, if hypertension is ticked "yes" and/or the systolic BP is ≥ 160mmHg
** Alcohol abuse is defined as ≥2 drinks per day

If one of the variables that is contributing to the HAS-BLED Score is missing, the score is not calculated.

The maximum of the HAS-BLED Score is 9 points. A categorisation into low / medium / high risk is given by:

Range	Risk
0 or 1	low
2	medium
3 or more	high

7.4.2.2 CHA_2DS_2-VASc Score

The CHA_2DS_2-VASc Score is based on eight variables which contribute (if fulfilled) to the score by each point:

Risk Factor / Variable	Points
Congestive heart failure/LV dysfunction*	1
Hypertension**	1
Age > 75	2
Diabetes Mellitus	1
Stroke or TIA or thromboembolic event	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or complex aortic plaque)	1
Age 65 – 74 y	1
Sex **c**ategory (female gender)	1

* Congestive heart failure / LV dysfunction is defined as present, if chronic heart failure is ticked "yes"
** Hypertension is defined as present, if hypertension is ticked "yes"

If one of the variables that is contributing to the CHA_2DS_2-VASc Score is missing, the score is not calculated.

The maximum of the CHA_2DS_2-VASc Score is 9 points. A categorisation into low / medium / high risk is given by:

Range	Risk
0	low
1	medium
2 or more	high

7.4.3 Scoring of questionnaire data (AFEQT)

Symptom subscale score

In a first step, the levels of the 7 answer categories (equal to the order of appearance) for the 4 questions contributing to the Symptom subscale (i.e. questions 1, 2, 3, 4) are coded as follows:

level 1 (*not at all bothered OR I did not have this symptom*) → 1

level 2 (*hardly bothered*) → 2

level 3 (*a little bothered*) → 3

level 4 (*moderately bothered*) → 4

level 5 (*quite a bit bothered*) → 5

level 6 (*very bothered*) → 6

level 7 (*extremely bothered*) → 7

In a second step, using the assigned values the Symptom subscale is calculated as follows:

$$100 - \left[\frac{(\text{sum of severity for questions 1, 2, 3, and 4 answered - number of questions answered}) \times 100}{(\text{total number questions answered} \times 6)}\right]$$

Daily Activities subscale score

In a first step, the levels of the 7 answer categories (equal to the order of appearance) for the 8 questions contributing to the Daily Activities subscale (i.e. questions 5, 6, 7, 8, 9, 10, 11, 12) are coded as follows:

(a) Questions 5 and 6:

level 1 (*not at all limited)* → 1

level 2 (*hardly limited*) → 2

level 3 (*a little limited*) → 3

level 4 (*moderately limited*) → 4

level 5 (*quite a bit limited*) → 5

level 6 (*very limited*) → 6

level 7 (*extremely limited*) → 7

(b) Questions 7 to 12:

level 1 (*no difficulty at all)* → 1

level 2 (*hardly any difficulty*) → 2

level 3 (*a little difficulty*) → 3

level 4 (*moderate difficulty*) → 4

level 5 (*quite a bit of difficulty*) → 5

level 6 (*a lot of difficulty*) → 6

level 7 (*extreme difficulty*) → 7

In a second step, using the assigned values the Daily Acivities subscale is calculated as follows:

$$\mathbf{100} - \left[\frac{(\text{sum of severity for questions 5, 6,7, 8, 9, 10, 11, and 12 answered - number of questions answered}) \text{ X } 100}{(\text{total number questions answered X } 6)}\right]$$

Treatment Concern subscale score

In a first step, the levels of the 7 answer categories (equal to the order of appearance) for the 6 questions contributing to the Symptom subscale (i.e. questions 13, 14, 15, 16, 17, 18) are coded as follows:

level 1 (*not at all bothered* → 1

level 2 (*hardly bothered*) → 2

level 3 (*a little bothered*) → 3

level 4 (*moderately bothered*) → 4

level 5 (*quite a bit bothered*) → 5

level 6 (*very bothered*) → 6

level 7 (*extremely bothered*) → 7

In a second step, using the assigned values the Treatment Concern subscale is calculated as follows:

$$\mathbf{100} - \left[\frac{(\text{sum of severity for questions 13, 14, 15, 16, 17, and 18 answered - number of questions answered}) \text{ X } 100}{(\text{total number questions answered X } 6)}\right]$$

Treatment Satisfaction subscale score

In a first step, the levels of the 7 answer categories (equal to the order of appearance) for the 2 questions contributing to the Symptom subscale (i.e. questions 19, 20) are coded as follows:

level 1 (*extremely satisfied)* → 1

level 2 (*very satisfied*) → 2

level 3 (*somewhat satisfied*) → 3

level 4 (*mixed with satisfied and dissatisfied*) → 4

level 5 (*somewhat dissatisfied*) → 5

level 6 (*very dissatisfied*) → 6

level 7 (*extremely dissatisfied*) → 7

In a second step, using the assigned values the Treatment Satisfaction subscale is calculated as follows:

$$100 - \left[\frac{(\text{sum of severity for questions 19 and 20 answered - number of questions answered}) \text{ X } 100}{(\text{total number questions answered X } 6)}\right]$$

Overall AFEQT score

In a first step, the levels of the 7 answer categories (equal to the order of appearance) for the 20 questions contributing to the Symptom subscale (i.e. questions 1 to 20) are coded as follows:

(a) Questions 1 to 4:

level 1 (*not at all bothered OR I did not have this symptom*) → 1

level 2 (*hardly bothered*) → 2

level 3 (*a little bothered*) → 3

level 4 (*moderately bothered*) → 4

level 5 (*quite a bit bothered*) → 5

level 6 (*very bothered*) → 6

level 7 (*extremely bothered*) → 7

(b) Questions 5 to 6:

level 1 (*not at all limited)* → 1

level 2 (*hardly limited*) → 2

level 3 (*a little limited*) → 3

level 4 (*moderately limited*) → 4

level 5 (*quite a bit limited*) → 5

level 6 (*very limited*) → 6

level 7 (*extremely limited*) → 7

(b) Questions 7 to 12:

level 1 (*no difficulty at all)* → 1

level 2 (*hardly any difficulty*) → 2

level 3 (*a little difficulty*) → 3

level 4 (*moderate difficulty*) → 4

level 5 (*quite a bit of difficulty*) → 5

level 6 (*a lot of difficulty*) → 6

level 7 (*extreme difficulty*) → 7

(c) Questions 13 to 18:

level 1 (*not at all bothered* → 1

level 2 (*hardly bothered*) → 2

level 3 (*a little bothered*) → 3

level 4 (*moderately bothered*) → 4

level 5 (*quite a bit bothered*) → 5

level 6 (*very bothered*) → 6

level 7 (*extremely bothered*) → 7

(d) Questions 19 to 20:

level 1 (*extremely satisfied)* → 1

level 2 (*very satisfied*) → 2

level 3 (*somewhat satisfied*) → 3

level 4 (*mixed with satisfied and dissatisfied*) → 4

level 5 (*somewhat dissatisfied*) → 5

level 6 (*very dissatisfied*) → 6

level 7 (*extremely dissatisfied*) → 7

In a second step, using the assigned values the Overall AFEQT score is calculated as follows:

$$100 - \left[\frac{(\text{sum of severity for all questions answered} - \text{number of questions answered}) \text{ X } 100}{(\text{total number questions answered X } 6)}\right]$$

7.5 Replacement of Data

7.5.1 Replacement of missing values

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. If Note to

Files arises after database closure (baseline data base lock or final database lock) that relate to data analysis, the data is changed accordingly for analysis.

According to the Clinical Investigational Plan, missing values will not be replaced for any of the parameters in the statistical analysis. Only observed cases will be evaluated.

7.5.2 Replacement of outliers

In general, outliers are evaluated as reported. In the event of highly implausible values (in the sense of extreme outliers) documented in the database after completion of data validation the following approach is used:

For some baseline variables (e.g. age, weight, height) as well as for vital signs so-called plausibility ranges will be defined (Table 3).

Observed values that are not within these ranges are set to missing within the analysis datasets. The intention of these ranges is to set them as wide as possible, so that only values that are obviously impossible (e.g. age of 150 years or systolic blood pressure of 20 mmHg) are set to missing. Borderline values confirmed by the investigator within a query will not be set to missing.

The definition of the ranges is always set in consultation with a medical expert. An appropriate documentation of the implausibility ranges is given in the following table of this SAP according to the ranges in the Data Validation Plan.

Table 3: Ranges

Value	Range
Height	90 - 250 cm
Weight	30 - 500 kg
BMI (automatically calculated)	15 - 40
Age	18 - 120 years
Catheter PV cryo ablation - Total no.	1 - 4
Catheter PV rf ablation - Total no.	1 - 4
Catheter PV 3D RF ablation - Total no.	1 - 4
Number of pharmalogical cardioversions	1 - 99 Total no.
Number of electrical cardioversions	1 - 99 Total no.
Number of admissions	1 - 9 Total no.
Number of drinks/day	5 - 99
AF burden (optional)	0 - 100 %
Documented LVEF	15 - 70 %
Documented anteroposterior left aterial diameter	0 - 100 mm
INR value	0,5 - 9

General time of the procedure	30 - 300 min
LSPV	0 - 40 no.
LIPV	0 - 40 no.
LCPV	0 - 40 no.
RSPV	0 - 40 no.
RIPV	0 - 40 no.
RMPV	0 - 40 no.
Other accesery vein	0 - 40 no.
Number of pharmalogical cardioversions	1 - 20 Total no.
Number of electrical cardioversions	1 - 20 Total no.
Documented LVEF	0 - 100 %
Number of pharmalogical cardioversions	1 - 99 Total no.
Number of electrical cardioversions	1 - 99 Total no.
AF burden	0 - 100 %

7.6 Self-Evident Corrections

Self-evident corrections will not be implemented in the raw data but on basis of the analysis data sets. They are described in the Data Validation Plan.

8 Descriptive Statistics

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, which should be finalized prior to interim analysis and need to be finalized prior final analysis.

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.

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.

Continuous 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, 5^{th} and 95^{th} percentile, lower and upper quartile (see SAP Appendix A).

Time-to-event data is planned to be analysed via a Cox proportional hazard regression model presenting hazard ratios and the corresponding 95% CI. In addition, Kaplan-Meier

curves may be presented for the time-to-event data. 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. Event rates will be calculated for 3, 6, 9 and 12 months after first documented procedure and may be displayed graphically.

To measure statistical differences in continuous or dichotomous/ multinomial variables between baseline and 12 month FU non-parametric (e.g. Friedman's Chi-Square Test, McNemar's Test) will be utilized. The test is only performed if the variable is not missing at admission and discharge.

A biometrical report including descriptive statistics of all relevant documented parameters will be generated for the overall patient population as well as for each participating country (SAP chapter 8.7). Depending on the variable(s) of interest, additional selection criteria for subjects (e.g. subgroup analyses) considered in specific analyses may be used, if considered useful during the statistical analysis (SAP chapter 8.6).

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 clinical study report[1].

In order to assess the effects of patients lost to follow-up, percentages of dropouts and reason for loss to follow-up 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.

Additionally, adequate graphs (e.g. bar charts, box-whisker plots) may be presented to summarize the results for some parameters. Further descriptive statistical analyses will be carried out, e.g. correlation analysis (SAP chapter 8.8).

8.1 Statistical analyses for the main objective

8.1.1 Estimate Phased RFA 12 month success rate

Success rate estimated as the time to first AF re-occurrence event from the first documented procedure. Data about AF events will be collected since the first documented procedure, including 90 days of the "blanking period" and closes at 12 months FU. If no AF events occur during the follow-up period (considering the "blanking period") up to 12 (+2) months, the case is considered to be "event-free". Calculations will be done for exact 12 months (351 days) after first documented procedure.

Main objective will be calculated for the BAS, FAS and EFAS (see chapter 4 and Appendix B). A successful first documented procedure (successfulness by PVI confirmation) is the basis to calculate the main objective. Patients with a procedure during the "blanking

[1] in the service agreement #2 refers to the final report, which is one and the same document for this study

period" of 90 days after first documented procedure will be excluded from main objective calculations.

Predefined AF re-occurrence definition from CIP Version 2.0 will not be applied to calculate the main objective. Further analysis might be used to estimate Phased RFA success rate considering (re-)occurring left Afl events.

AF re-occurrence event defined as:

- AF pharmacological and/or electrical CV
- AF more the 30 sec on ECG/EGM
- AF less than 30 sec in combination with AF symptoms
- Re-ablations for AF

For this analysis adjudicated AE data and coded AE data (free text fields) will be used. AF re-occurrence event rate will be estimated with and without the use of antiarrhythmic drugs at time of the 12 month follow-up. AF re-occurrence rates will be calculated for patients from BAS and FAS (Appendix B) which need to have a signed 12 month FU / 12 month FU by phone form by definition. AF re-occurrence is defined as the first event of AF re-occurrence event and their related date information based on the following eCRF forms and data fields:

Table 4: Main objective variables at 12MFU / General FU form

eCRF field	Related date field	Related FID's annotated eCRF (V1.3, V1.4)
Reason for visit: AF re-occurrence	Date of visit	F11000050 F11000010
Re-ablation reason: Due to AF-occurrence	Date of visit	F11000070 F11000010
History of arrhythmias since last visit: AF	Date of first occurrence	F12000012 F12000050
History of arrhythmias since last visit: Re-ablation for AF	Date of re-ablation for AF	F12000060 F12000070
CVD hospitalizations during last visit: AF	Date of first admission	F15000020 F15000030

Table 5: Main objective variables at 12MFU by phone form

eCRF Field	Related date field	Related FID's annotated eCRF (V1.3, V1.4)
History of arrhythmias since last visit: AF	Date of first occurrence	F13000010 F12000050
History of arrhythmias since last visit: Re-ablation for AF	Date of re-ablation for AF	F12000060 F12000220
CVD hospitalizations during last visit: AF	Date of first admission	F15000010 F15000020_1 F15000030

Table 6: Main objective variables at AE form

eCRF Field	Related date field	Related FID's annotated eCRF (V1.3, V1.4)
Other diagnostics: ~"AF"	Date of AE	F31000010_88 F30000090 F30000010

8.1.2 Methodology for analysing the main objective

Any AF re-occurrence event (Tables 5, 6 and 7) during the "blanking period" will be not be considered. "Blanking period" starts with the day of the first documented procedure and ends at exact 90 days. The first documented date of AF re-occurrence will be set as the event date. "Blanking period" for patients with additional procedure(s) at any time will not be started newly, they will be considered as "not-event free" at time of the first additional procedure.

Freedom from AF re-occurrence at 12 months will be estimated using Kaplan-Meier methods (time-to-first-event-analysis). A point estimate at the date of 12MFU post first documented 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. For patients without a reported AF re-occurrence event, those patients will be censored. In this case, the right-censoring time will be set to the last study contact date. Main objective Kaplan-Meier estimation results will be displayed in percentages at 12 months (351 days) after first documented procedure. Estimated AF re-occurrence rates by month (at the end of month 3 to 11 after first documented-procedure) will be calculated and displayed as well. For group comparisons Log-Rank test will be applied. Also, Hazard ratios and 95% confidence intervals will be shown (for group comparisons, please see SAP chapter 8.6). For Kaplan-Meier estimation, numbers at risk will be displayed for reasonable points in time.

Re-occurrence of AF during 12 months (considering the "blanking period") will also be analysed via Cox proportional hazard regression model presenting hazard ratios and the corresponding 95% CI. Independent variables will be determined by Phased RFA procedure experts or physicians. Cox modelling for AF re-occurrence will be done for all predefined subgroups (FAS patients) where the analysis scope is the 12 month outcome (SAP chapter 8.6.1). Further Cox modelling (e.g. for multiple AF events) may be applied.

8.2 Statistical analyses for additional objective

8.2.1 Estimate Phased RFA procedure safety

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

Adverse events (AE) including their relatedness to the respective procedure, are documented starting from the first documented procedure until the 12 month FU. For this analysis only adjudicated AE data (SUO form) and coded AE data (from free text fields) will be used. In addition, TIA/Stroke events will be taken from general FU forms to calculate procedure safety. Analysis will be performed at 30 days and at 12 months after procedure.

If no adverse event was documented within the 12 month FU period, the patient or the procedure is considered to be "free of AE". AEs are documented in the AE form, whereby distinctions in relatedness to which procedure (index phased RFA, repeated phased RFA or phased RFA re-ablation) will be made. Phased RFA procedure relatedness will also be taken from the AE form (Relatedness to Phased RFA procedure = related). The documented date of the AE will be used to set the point in time. For analysis purposes, phased RFA procedure safety will be calculated for first documented procedures (on procedure and patient level), separated for additional procedures (on procedure level) and for patients with additional procedures (on patient level).

Procedure safety will be calculated for procedures that have been carried out (number of RF applications per patient > 0) and disregarding procedure successfulness. This study objective will be calculated for the BAS and the FAS (Appendix B) for patients with signed eCRF.

Further analysis might be performed, e.g. procedure safety for using PVAC GOLD solely or not PVAC GOLD solely (using other catheter or using adjunctive devices).

Table 7: Procedure safety variables at AE form

AE due to definition	**eCRF field: AE description**	**Related FID's** annotated eCRF (V1.3, V1.4)
Vascular access complication	Vascular access complication • Hematoma or • Arterio-venous fistula or • Femoral artery pseudoaneurysm	F31000010_6
Cardiac tamponade	Pericardial damage • Tamponade or • Pericardial Effusion	F31000010_8
Stroke	Stroke	F31000010_2
Esophageal injury	Atrioesophageal damage • Injury or • Fistula	F31000010_9
Phrenic nerve injury	Phrenic nerve damage • Injury or • Palsy or • Paralysis	F31000010_7
PV stenosis	PV stenosis • Symptomatic or • Asymptomatic • % of diameter of stenosis ▪ ≤ 50% or ▪ >50% or ▪ NA	F31000010_1 F31000030
Re-entrant tachycardia arrhythmias arising from ablations	Other (diagnosis) Description field	F31000010_88 F31000090
Mainly left Afl	Left Afl	F31000010_11
Other diagnostics: text complies to AEs above, text will be coded	Free text field	F31000010_88 F30000090 F30000010

Table 8: Procedure safety variables at FU form

AE due to definition	eCRF field: AE description	Related FID's annotated eCRF (V1.3, V1.4)
Stroke	• TIA/Stroke	F15000140 F15000150

8.2.2 Methodology for analysing the procedure safety

The number of patients with reported device and procedure related events will be summarized as a binomial variables for each event and combined; number and percentage of events and patients with events (up to 12 month after first documented procedure). Additionally, Kaplan-Meier estimations (time-to-first-event analysis) will be used to summary the timing of the occurrence of safety events through 30 days and 12 months (351 days) after first documented procedure. Time from onset to resolution of events will also be presented. Further strata may be applied for analysis (e.g. reason for ablation: index, repeated, re-ablation, left Afl).

8.3 Statistical analyses for ancillary objectives

According to Appendix B, these analyses will be performed for the Baseline Analysis Set and Full Analysis Set. If not described otherwise, ancillary objectives will be analysed using methods of descriptive statistics (SAP chapter 8).

8.3.1 Characterize the acute procedural success rate

Success rates will be calculated for all documented procedures combined (patient level). Also, procedure success rates will be provided for first documented procedures, additional procedures, regular cases and training cases, separately. Success rates will also be shown per vein.

Success will be calculated for procedures that have been attempted (number if RF applications per patient > 0). Success rates will be provided for PVAC GOLD solely procedures (ancillary objective) and additionally for not PVAC GOLD solely procedures (using other catheter and/or using adjunctive devices).

If RF applications per patient, consumables (Phased RFA catheters used), successfulness and PV confirmation (exit or entrance block) was not verified for the procedure, the data will not be used for analysis. Consumables and procedure success will be taken from the procedure form. Relatedness of Phased RFA will be taken from AE form.

The procedure is considered successful if:

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

This combined endpoint (variables linked via "and operation") is applicable, if all conditions are available and complied.

Because of different procedure forms (eCRF V1.3 and eCRF V1.4), PVI achievement by PVAC GOLD only is assumed for patients documented by eCRF V1.3 as follows:

- [F21000010] Phased RFA catheter used: only PVAC GOLD is ticked, and
- [F22000010] to [F22000060] PVI confirmation: exit block and/or entrance block are ticked, and
- [F20001000] Number of RF applications per patient > 0

Unsuccessfulness per vein is considered, if the vein is not isolated or not verified. Percentages for success will be shown per vein for patients treated with PVAC GOLD solely. Precondition is that the number of RF applications per patient is greater than zero.

PVI achievement by PVAC GOLD only is defined for patients documented by eCRF V1.4 as follows:

- [F21000010] Phased RFA catheter used: only PVAC GOLD is ticked, and
- [F22000062] Where all PVs isolated at the end of the procedure = yes, and
- [F22000066] Where all PVs isolated by using PVAC only = yes, and
- [F21000010] Number of RF applications per patient > 0

Unsuccessfulness per vein is considered, if the vein is not isolated or not verified. Percentages for success will be shown per vein for patients treated with PVAC GOLD, all PVs were isolated at the end of the procedure = no and all PVs isolated by using PVAC only = no.

Table 9: Procedure success variables from Procedure and AE form

Objective section	**Definition (used variables)**	**Related FID's** annotated eCRF (V1.3, V1.4)
Procedure attempt was not declined due to technical issues related to Phased RFA system	Procedure form: Date of procedure Phased RFA procedure successful? No – Due to AE AE form: Date of AE Was the event related to technical issues?* Related/Possibly related	F20000010 F22000180 F22000190 F30000010 F30000070
Only PVAC catheter(s) used to achieve PVI	Procedure form: Phased RFA catheters used PVAC GOLD (solely) Number of RF applications per patient > 0 Were all PVs isolated at the end of the procedure Were all PVs isolated by using only PVAC	eCRFV1.3/V1.4 F21000010 F20001000 eCRFV1.4 only F22000062 F22000066

All accessible PVs were isolated (entrance and/or exit block confirmation per vein)	Were all accessible PVs isolated at the end of the procedure entrance block and/or exit block Exit block and/or Entrance block	eCRFV1.3/V1.4 F22000010 F22000020 F22000030 F22000040 F22000050 F22000060

* Precondition: If the documented AE is related to technical issues with Phased RFA system components, the date of the latest procedure must be ≤ date of the AE. For patients with more > 1 procedure, the latest procedure will be the related procedure.

8.3.1.1 Methodology for analysing the acute procedural success rate

Acute procedural success rate will be reported as frequency and percentages. 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.

8.3.2 Assess Phased RFA efficiency

Phased RFA efficacy data will be shown for all documented procedures combined (patient level). Also, phased RFA efficacy will be provided for first documented procedures, additional procedures, regular cases and training cases, separately.

The parameters to measure the efficiency:

- Procedure duration
- Laboratory occupancy duration
- Fluoroscopy time
- Phased RFA consumables used
- Adjunctive devices (mapping or navigation systems)

Table 10: Phased RFA efficiency variables from procedure form

Objective section	**Definition (used variables)**	**Related FID's** annotated CRF (V1.3, V1.4)
Procedure duration	General time of the procedure	F20000611
Laboratory occupancy duration	Time patient delivered to the Catheter Lab Time patient left the Catheter Lab	F20000420 F20000610
Fluoroscopy time	Total fluoroscopy time	F20000620
Phased RFA consumables used	General number of catheters used Phased RFA catheters used Other (free text field)	F21000005 F21000010 F21000020
Adjunctive devices (mapping or navigation systems)	Adjunctive devices used during the procedure Other (free text field)	F21000040 F21000050

Phased RFA efficiency will be analysed for all implemented procedures only (number if RF applications per patient > 0). Time data will be shown for PVAC GOLD solely and using different catheters or adjunctive devices. Additionally, it will be distinguished between reasons of ablation (index, repeated, re-ablation, left AfI).

8.3.3 Characterize the peri-procedural anticoagulation therapy

Peri-procedural anticoagulation therapy data will be shown for all documented procedures combined (patient level). Also, peri-procedural anticoagulation therapy will be provided for first documented procedures, additional procedures, regular cases and training cases, separately.

The parameters of interest:

- 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

Table 11: Peri-procedural anticoagulation therapy variables from baseline, procedure and AE form

Objective section	Definition (used variables)	Related FID's annotated eCRF (V1.3, V1.4)
Activated clotting time (ACT) during the procedure	Highest ACT during procedure Lowest ACT during procedure	F20000300 F20000320
Peri-procedural INR	Latest measured INR INR value Date of INR test	F20000260 F20000270 F20000280
Oral anticoagulant therapy/LMWN before, during and after the procedure	Procedure form: Was oral anticoagulant discontinued before the procedure How many hours prior to procedure Was LMWH administered before the procedure Instead of oral Anticoagulants In addition to the oral anticoagulants Baseline form (prior procedure): Anticoagulation Medication Specify (free text field) Procedure form (after procedure): Was anticoagulation continued after the procedure How long after procedure Procedure form (after procedure/at discharge): Anticoagulation Medication Specify (free text field)	 F20000210 F20000220 F20000230 F20000240 F20000250 F17500100 F17500120 F23000060 F23000070 F19500100 F19500120

TIA/stroke related to study Phased RFA procedure	Procedure form: Date of procedure Phased RFA procedure successful? No – Due to AE AE form: Date of AE	F20000010 F22000180 F22000190 F30000010 F31000010_2 F31000010_3

8.3.4 Describe single catheter PVAC GOLD utilization in persistent AF

Single PVAC GOLD utilization data will be shown for all documented procedures combined (patient level). Also, single PVAC GOLD utilization will be provided for first documented procedures, additional procedures, regular cases and training cases, separately.

Single catheter PVAC GOLD utilization means here, that only PVAC GOLD was used during the procedure, regardless of using sheaths. No adjunctive devices were used. For this ancillary objective, only patients with persistent AF will be analysed.

The parameters of interest are:

- Phased RFA catheters used during the procedure
- Indication for Phased RFA
- Location of linear lesions or substrate modifications
- Atrial CV
- AF/ left Afl recorded on ECG/EGM
- AF re-ablations

Table 12: PVAC GOLD utilization variables from baseline and procedure form

Objective section	**Definition (used variables)**	**Related FID's** annotated eCRF (V1.3, V1.4)
Phased RFA catheters used during the procedure	General number of catheters used Phased RFA catheters used Other (free text field) From procedure form	F21000005 F21000010 F21000020
Indication for Phased RFA	Indication to schedule Phased RFA (AF type) If "Persistent AF" From baseline form	F10000110 F10000113
Location of linear lesions or substrate modifications	Were any non-PVI lesions performed Substrate Modification = Lines Location From procedure form	F20001010 F20001040 F20001020

Atrial CV	Cardioversion(s) for AF in the last 12 months Latest date of CV(s) specify CV From baseline form	F13000710 F13000720 F13000740 F13000750 F13000770

8.3.5 Evaluate QoL (AFEQT) dynamic at 12 month FU

Quality of Life analysis will be done for all available subjects. Therefore, completed AFEQT questionnaire at baseline and at 12 month FU will be used. With it, single scales and AFEQT score will be analysed at baseline and at 12 months. Also, absolute and relative differences in AFEQT score between baseline and 12 months will be displayed. Score calculations are described in SAP chapter 7.4.3, rules for analysis in SAP chapter 6.3.

8.4 Interim analysis

Interim analysis (see CIP Version 2.0), based on study data reported prior to the final report, may be completed and utilized for publication. After documenting all intended first documented procedures and pass the query solving process for baseline data, interim database lock will be used to set a locked data set for this analysis. Analysis sets, analysis tables and predefined comparison groups for interim analysis are displayed in Appendix B and D. Ancillary objectives (SAP chapter 8.3.1 to 8.3.4) will be calculated for this data status. Besides, all other parameters from baseline and first documented procedure will be shown. For details see Appendix B. Data analysis will be in descriptive manner. No adjustments for alpha are necessary as no hypotheses are being tested.

8.5 Final analysis

At the end of this study and after the final data base lock, final tables including study objectives (Appendix B), subgroup analysis, comparison group analysis, graphical analysis and benchmark analysis will be performed. Data analysis will be in descriptive manner. No adjustments for alpha are necessary as no hypotheses are being tested.

8.6 Analysis of group comparisons and subgroups

To evaluate special subjects, predefined subgroup analysis and predefined group comparisons will be performed. Subgroup and group comparisons will be done at the end of this study. If needed, further analysis can be carried out.

8.6.1 Analysis of subgroups

Descriptive subgroup reports will be listed in Appendix C.

8.6.2 Analysis of comparison groups

Group comparison will be provided including non-parametric statistical tests and odds ratios with 95% CI (two-group comparison) for all parameters. In Appendix D descriptive reports are listed.

8.7 Benchmark reports

The benchmark reports are a comparison of one single unit (site or country) to the entire group of all other participating units. These benchmark reports are designed to be used as quality control for the participating sites and to describe country differences. Benchmark reports will be provided for:

- Participating site vs. all other sites
- Participating country vs. all other countries

The BAS will be the analysis population. Statistical reports (descriptive statistics) will be provided including all parameters from Baseline, First documented procedure, Additional procedure, GFU and 12MFU, but due to data protection no data from the Adverse Event form. The benchmark reports will be listed in tabular form and, depending on the variable type, the statistical output will include numbers and percentages, mean ± SD, Odds ratio with 95% CI for all available parameters.

8.8 Graphical analysis

Graphical analysis will be provided for final analysis. The graphs will be created using SAS. Predefined graphical analysis will be done for the following topics and strata. Additional graphical analyses can be carried out after database closure.

Table 13: Predefined graphical analysis

Target variable	Analysis method	Patients set or strata
Main objective: AF re-occurrence by study definition during 12 months Additional analysis: AF re-occurrence with and without considering the "blanking period" of 90 days AF re-occurrence up to 14 month (end of FU period) after first documented procedure	Kaplan-Meier estimation (time-to-first-event)	• BAS, FAS, EFAS • AF type
Additional objective: Phased RFA procedure safety	Kaplan-Meier estimation (time-to-first-event)	• FAS • Reason for ablation: index, repeated, re-ablation, left Afl
Anticoagulation medication before /during/ after/ at 12months FU	Graphical (stacked) bar analysis	• FAS, EFAS • LAAO implantation
Analysis of procedure time by • Site • Operator	Box-whisker plots	• FAS, EFAS
Correlation between Anticoagulation and • INR • ACT • Stroke	Suitable correlation methods	• FAS
Correlation between AF re-occurrence and • BMI • Age	Suitable correlation methods	• BAS, FAS, EFAS
COX regression analysis (SAP chapter 8.1.2)	Forest plot (for HR + CI)	• FAS, EFAS
Analysis of DAP - by site	Box-whisker plots	• BAS

9 References

Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012 Nov 1;33(21):2719–47.

Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–272.

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093–1100.

Appendix A: Table specifications (examples)

Table specification for analysis tables (numbers, metric and dichotomous variables)

Variable	**Specification**	**Format**	**Nominator (if applicable)**	**Denominator (if applicable)**
Number of patients in APS	All patients that met the criteria of the APS	Integer		
Age		None		
Mean ± SD, N	mean ± standard deviation (format: 2 decimal places), number of patients with age values	2 decimal places, Integer		
Median (Q1-Q3)	median and interquartile range in brackets (format: 2 decimal places)	2 decimal places		
5th and 95th Percentile	median and interquartile range in brackets (format: 2 decimal places)	2 decimal places		
Min, Max	minimal and maximal value (format: 2 decimal places)	2 decimal places		
Male gender	percentage of male patients	2 decimal places	male patients	all patients with gender information

Appendix B: Analysis tables, Study objectives and Analysis sets

eCRF SEGMENTS	eCRF CHAPTERS/ ANALYSIS TABLES	STUDY OBJECTIVES	ANALYSIS SETS FOR INTERIM ANALYSIS	ANALYSIS SETS FOR FINAL ANALYSIS
BASELINE	Enrolment		APS, BAS	APS, BAS, FAS, EFAS
	Indication/Admission		APS, BAS	APS, BAS, FAS, EFAS
	Demographics		BAS	BAS, FAS, EFAS
	History of CVD		BAS	BAS, FAS, EFAS
	History of AF		BAS	BAS, FAS, EFAS
	Symptoms		BAS	BAS, FAS, EFAS
	Concomitant Diseases		BAS	BAS, FAS, EFAS
	Diagnostics		BAS	BAS, FAS, EFAS
	Medications List		BAS	BAS, FAS, EFAS
	AFEQT		BAS	BAS, FAS, EFAS
	Anticoagulation (before/during first documented procedure)	ANCILLARY OBJECTIVE	BAS	BAS, FAS, EFAS
FIRST DOCUMENTED PROCEDURE	Administrative information		APS, BAS	APS, BAS, FAS, EFAS
	Procedure summary information	ANCILLARY OBJECTIVE	BAS	BAS, FAS, EFAS
	Consumables		BAS	BAS, FAS, EFAS
	PVI confirmation		BAS	BAS, FAS, EFAS
	Hospital discharge		APS, BAS	APS, BAS, FAS, EFAS
	Medication list at discharge		BAS	BAS, FAS, EFAS
ADDITIONAL PROCEDURE(S)	Administrative information		-	BAS, FAS, EFAS
	Procedure summary information	ANCILLARY OBJECTIVE	-	BAS, FAS, EFAS
	Consumables		-	BAS, FAS, EFAS
	PVI confirmation		-	BAS, FAS, EFAS
STUDY EXIT	Study exit		APS, BAS	APS, BAS, FAS, EFAS
AE	Administrative Information/Adverse Event	ADDITIONAL OBJECTIVE	-	BAS, FAS, EFAS
	Relatedness of the AE		-	BAS, FAS, EFAS
	Description of AE/AEAC		-	BAS, FAS, EFAS
GENERAL FU	Administrative Information		-	BAS, FAS, EFAS
	History of Arrhythmias since the last visit		-	BAS, FAS, EFAS

	Diagnostics		-	BAS, FAS, EFAS
	Symptoms		-	BAS, FAS, EFAS
	Hospitalizations		-	BAS, FAS, EFAS
	Medication List		-	BAS, FAS, EFAS
12MFU VISIT / 12MFU BY PHONE	Administrative Information		-	BAS, FAS, EFAS
	History of Arrhythmias since the last visit	MAIN OBJECTIVE	-	BAS, FAS, EFAS
	Diagnostics		-	BAS, FAS, EFAS
	Symptoms		-	BAS, FAS, EFAS
	Hospitalizations		-	BAS, FAS, EFAS
	Medication List		-	BAS, FAS, EFAS
	AFEQT	ANCILLARY OBJECTIVE	-	BAS, FAS, EFAS

Appendix C: Subgroup analysis

Predefined subgroups (V1.0)

Subgroup description	**Analysis set, additional inclusion or exclusion criteria**	**Tables and scope for analysis**
Indication to schedule Phased RFA: Paroxysmal AF	FAS, EFAS incl.: --- excl.: ---	Baseline First documented procedure Additional procedure 12MFU
Indication to schedule Phased RFA: Persistent AF	FAS, EFAS incl.: --- excl.: ---	Baseline First documented procedure Additional procedure 12MFU
Indication to schedule Phased RFA: Longstanding persistent AF	FAS, EFAS incl.: --- excl.: ---	Baseline First documented procedure Additional procedure 12MFU
Successful first documented procedure	FAS, EFAS incl.: --- excl.: ---	Baseline First documented procedure Additional procedure 12MFU
Non-successful first documented procedure	FAS, EFAS incl.: --- excl.: ---	Baseline First documented procedure Additional procedure 12MFU
First documented procedure: PVAC GOLD solely	FAS, EFAS incl.: Phased RFA catheters = PVAC GOLD, general number if catheters used = 1 excl.: adjunctive devices used during the procedure, disregarding sheaths used	First documented procedure Additional procedure GFU 12MFU
First documented procedure: PVAC GOLD + other catheters	FAS, EFAS incl.: Phased RFA catheters = PVAC GOLD, general number if catheters used > 1, additional Phased catheter used (MAAC, MASC and/or Other) excl.: adjunctive devices used during the procedure, disregarding sheaths used	First documented procedure Additional procedure GFU 12MFU
First documented procedure: Phased RFA catheter solely	FAS, EFAS incl.: Phased RFA catheters used, general number if catheters used = 1 excl.: adjunctive devices used during the procedure, disregarding sheaths used	First documented procedure Additional procedure GFU 12MFU
First documented procedure: Phased RFA catheter + adjunctive devices	FAS, EFAS incl.: Phased RFA catheters = PVAC GOLD, general number if catheters used > 1, additional Phased catheter used (MAAC, MASC and/or Other), adjunctive devices used during the procedure excl.: ---	First documented procedure Additional procedure GFU 12MFU
Procedure: Patients with multiple procedures	FAS, EFAS	Baseline First documented procedure Additional procedure

	incl.: patients with > 1 documented procedure excl.: ---	GFU 12MFU
Baseline: Patient with AF surgery or ablations in history	FAS, EFAS incl.: prior AF surgery, status post ablation (endocardial, epicardial, Catheter PV, Phased RF, 3D RF or Other ablation technologies) excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU
Baseline: Patient without AF surgery or ablations in history	FAS, EFAS incl.: no prior AF surgery, no status post ablation (endocardial, epicardial, Catheter PV, Phased RF, 3D RF or Other ablation technologies) excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU
Baseline: Reveal implanted patients	FAS, EFAS incl.: ICM implantation - Reveal XT, Reveal LINQ or other excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU
First documented procedure: Anticoagulation in patients with LAAO	FAS, EFAS incl.: LAAO implantation, anticoagulation medication prior first documented procedure excl.: ---	Baseline First documented procedure 12MFU
First documented procedure: patients with LAAO	FAS, EFAS incl.: LAAO implantation excl.: anticoagulation medication prior first documented procedure	Baseline First documented procedure 12MFU
Patients with administrated at least one antiarrhythmic drug (except beta-blocker)	FAS, EFAS incl.: patients with >=1 antiarrhythmic medication (except beta-blocker) at any time of this study excl.: ---	Baseline First documented procedure GFU 12MFU
Patients without antiarrhythmic drug therapy	FAS, EFAS incl.: no antiarrhythmic medication at any time of this study excl.: ---	Baseline First documented procedure GFU 12MFU
First documented procedure: Patients with discontinued oral anticoagulation before the procedure	FAS, EFAS incl.: patients with oral anticoagulation prior to scheduled phased RFA and discontinued before first documented procedure excl.: ---	First documented procedure GFU 12MFU
First documented procedure: Patients with oral anticoagulation before the procedure	FAS, EFAS incl.: patients with oral anticoagulation prior to scheduled phased RFA and not discontinued before first documented procedure excl.: ---	First documented procedure GFU 12MFU
Patients lost to 12 month FU	APS, BAS incl.: patients w/o 12MFU excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU

Appendix D: Analysis of comparison groups

Predefined comparison groups (V1.0)

Comparison description	Analysis set, additional inclusion or exclusion criteria	Tables and scope for analysis	At time of Interim analysis	At time of Final analysis
Age <65, 65-74, ≥75	FAS, EFAS incl.: Age available excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU	-	X
Body Mass Index <18.5, 18.5 to <25, 25 to <30, ≥30	FAS, EFAS incl.: BMI available excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU	-	X
EHRA AF symptoms (at admission during the last 12 months) None, Yes – I "No", II "Mild", III "Severe", IV "Disabling"	FAS, EFAS incl.: AF symptoms available excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU	-	X
Gender Males, Females	BAS, FAS, EFAS incl.: Gender available excl.: ---	Baseline First documented procedure Additional procedure GFU 12MFU	X	X
First documented procedure Regular case, Training case	BAS, FAS, EFAS incl.: Regular or training case available excl.: ---	First documented procedure Additional procedure GFU 12MFU	X	X
Discharge after First documented procedure Patient discharged home, Transferred to another hospital, Death	FAS, EFAS incl.: Discharge available excl.: ---	First documented procedure Additional procedure GFU 12MFU	-	X
Adverse events Patients with AE during 12 months, Patients w/o AE during 12 months	FAS, EFAS incl.: Adjudicated events available excl.: ---	First documented procedure Additional procedure GFU 12MFU	-	X
Re-occurrence of AF Patients with re-occurrence AF, Patients w/o re-occurrence AF during 12 months	FAS, EFAS incl.: --- excl.: ---	Baseline First documented procedure GFU 12MFU	-	X
First documented procedure Phased RFA <40 min of fluoroscopy time vs. >= 40 min of fluoroscopy time	BAS, FAS, EFAS incl.: Fluoroscopy time available excl.: ---	First documented procedure Additional procedure GFU 12MFU	X	X
First documented procedure	BAS, FAS, EFAS	First documented procedure Additional procedure GFU 12MFU	X	X

General time of the procedure time <100 min vs. >=100 min	incl.: Total procedure time available excl.: ---			
Patients with more than 5 GFU vs. all other patients	BAS, FAS, EFAS incl.: --- excl.: ---	Baseline GFU 12MFU	-	X
Patients lost to 12MFU vs. not lost to 12MFU (according SAP chapter7)	BAS incl.: --- excl.: ---	Baseline GFU 12MFU	-	X
Analysis of missed data	BAS incl.: --- excl.: ---	Full tables set	-	X
DAP by country	BAS incl.: --- excl.: ---	Baseline	-	X
Fluoroscopy time by country	BAS incl.: --- excl.: ---	Baseline	-	X

Appendix E: Annotated eCRF V1.3 and V1.4

Appendix F: Follow-up Re-Assignment

Issue	Decision	Center-Patient-ID
12MFU outside 12MFU time window and GFU inside	Use GFU instead of 12MFU for analysis	3580-1222, 4497-335, 4497-337, 4497-345, 4497-1529, 9641-551
12MFU outside 12M time window and no GFU inside	Use 12MFU as GFU in 9-12M time window analysis	1946-1671, 1946-1674, 1946-1678, 1946-1679, 2737-1642, 3140-463, 3580-1444, 4608-1472, 5042-820, 5042-832, 5576-207, 5576-208, 5576-211, 5576-212, 5576-213, 5576-218, 5576-219, 5576-1191, 5576-1193, 7549-402, 7554-1319, 7626-859, 7626-860, 7626-861, 7626-865, 7626-1579
Duplicate 12MFUs (Visit and by Phone) inside 12M time window	Use 12MFU visit for 12M analysis and disregard 12MFU phone	8413-420
12MFU and GFU inside, events only in 12MFU and at most minor differences	Use 12MFU for 12M analysis and disregard GFU	3580-1735, 3730-190, 3730-195, 4497-339, 4497-350, 4497-903, 4497-909, 4497-911, 4497-920, 4497-1107, 4497-1109, 4497-1119, 4497-1123, 4497-1516, 4497-1714, 4497-1781, 4497-1789, 4497-1801, 4497-1803, 5658-175, 6021-633, 6807-86, 6979-497, 8533-147, 9641-1456, 9641-1457, 9641-1458, 9641-1461, 9641-1467
12MFU and GFU inside 12M time window, events only in GFU and at most minor differences	Transfer event details (e.g. AF-reoccurrence, Hospitalisation..) to 12MFU for analysis and disregard GFU	3354-42, 3730-181, 4497-1102, 4497-1118, 9641-1463, 9641-1464, 9641-2593
12MFU and GFU inside 12M time window, different events and minor differences in 12MFU and GFU	Use 12MFU for analysis and transfer events from GFU	4497-1126, 4497-1523, 5658-164, 6979-585, 9641-1455, 9641-2601

This Statistical Analysis Plan has been written with reference to:

ICH GCP E6: International Conference on Harmonisation Guideline for Good Clinical Practice

ICH GCP E9: International Conference on Harmonisation Statistical Principles for Clinical Trials

Directive 2001/20/EC

MPG Medizinproduktegesetz

MPKV Verordnung über klinische Prüfungen von Medizinprodukten