PROOF: Evaluating the **P**erformance of the KODEX-EPD C**R**y**O**balloon **O**cclusion **F**eature in patients with atrial fibrillation **(CLN-KODEX-0019)**

Clinical Investigation Plan

Protocol version:	4
Clinicaltrials.gov	NCT04293198
Issue Date:	15-Jul-20
Clinical Study Sponsor:	EPD Solutions (a/k/a Philips Medical Systems Nederland B.V.) Veenpluis 6 5684 PC, Best The Netherlands
(Revision History);	Version 1.0 2019 Dec 10
	Version 2.0 2020 Jan 21
	Version 3.0 2020 Jul 15
	Version 4.0 2022 Jan 31

Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol.
- I agree to conduct the study in compliance with the protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), patient privacy regulations and other applicable regulatory requirements.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.
- I agree to provide all required data and agree to source document verification of study data with patient's medical records.
- I agree to report serious and/or unanticipated and/or device related adverse events to Sponsor within 24 hours from occurrence.

_____
Site Name

_____
Principal Investigator Name

_____ _____
Signature Date

STUDY COLLABORATORS

Coordinating Investigators	Ronald Berger Johns' Hopkins University 600 North Wolfe Street Halsted 570 Baltimore, MD 21287, USA rberger@jhmi.edu +1 410 614 2751	Carlo De Asmundis UZ Brussel Laarbeeklaan 101 1090 Jette Brussel, Belgium Carlo.Deasmundis@uzbrussel.be +32(0)494 92 05 84

TABLE OF CONTENTS

Study Synopsis

STUDY TITLE	**PROOF**: Evaluating the **P**erformance of the KODEX-EPD C**RyO**balloon **O**cclusion **F**eature in patients with atrial fibrillation
STUDY PHASE	Post-market
INVESTIGATIONAL PRODUCT	KODEX-EPD System, KODEX-EPD data collection accessories
INDICATION	Patients with Atrial Fibrillation
OBJECTIVE	Performance of KODEX-EPD PV occlusion feature as compared to conventional venographic method of fluoroscopy with contrast dye in cryoballoon procedures that is used to guide the procedure. Performance will be calculated in terms of accuracy, sensitivity, specificity and positive and negative predictive values. In the blinded arm of the study, the operator will be blinded for the PV occlusion data on the KODEX-EPD system and this data will not be used for clinical guidance.
STUDY DESIGN	Prospective, multi-center, non-randomized, open label, double arm study
# OF SUBJECTS	The study will include a maximum of 20 patients per center at 2 centers in the blinded to KODEX arm of the study. An additional 25 patients will be included at UZ Brussel in the KODEX guided arm of the study.
STUDY DURATION	18 months
STUDY POPULATION	Arrhythmia patients scheduled to undergo a cryo balloon ablation procedure for their atrial fibrillation. Both male and female subjects who meet all eligibility criteria and give written informed consent will be enrolled in the study. *Inclusion criteria:* 1. Subject must be aged >18 years. 2. Subject must have signed a written Informed Consent form to participate in the study, prior to any study related procedures.

	3. Subject must be willing to comply with the protocol requirements. 4. Subject receives a de novo ablation procedure for treatment of atrial fibrillation. *Exclusion criteria;* Pregnant women.
STUDY VISIT SCHEDULE AND PROCEDURES	This is an acute study with no follow-up. **Before the procedure (Baseline)**: 1. Eligibility according to inclusion and exclusion criteria 2. Obtaining signed Informed Consent Form (ICF) 3. Demographics 4. Medical history 5. Physical examinations 6. Concomitant medications 7. Presence/history of atrial fibrillation 8. Previous and current treatments of atrial fibrillation **During procedure:** 1. Delivery of standard therapy. The study device will be used in the cryoballoon ablation procedure according to the instructions for use. PV occlusion will be assessed with the KODEX-EPD PV occlusion feature. - Blinded Arm; The physician will be blinded for the KODEX-EPD occlusion data and use conventional venographic method of fluoroscopy with contrast dye to guide the procedure. - KODEX guided Arm; the physician will use the KODEX-EPD occlusion data to guide the procedure 2. Confirmation of therapy. Confirm PV isolation using standard practice. 3. Adverse events Reporting.
PRIMARY ENDPOINTS	1. The accuracy, sensitivity, specificity and positive and negative predictive values of the KODEX-EPD PV occlusion feature as compared to conventional venographic method of fluoroscopy with contrast dye that will be used to guide the procedure. 2. The success of the freeze when freeze is initiated based on the assessment of the KODEX-EPD PV occlusion feature as compared to the success of the freeze when freeze is

	initiated based on the assessment with fluoroscopy and contrast dye.
SECONDARY/ EXPLORATORY ENDPOINTS	Procedure data collection: • KODEX-EPD data collection • Fluoroscopy system data collection • Fluoroscopy time • Fluoroscopy dose • Number of contrast dye injections • Contrast dye volume • Information on durability of the PV isolation. • Time to isolation (TTI)/Success of Isolation • Number of ablations per vein • Procedure time (skin to skin)
SPONSOR	EPD Solutions is the sole study sponsor. This study will be conducted according to US 21 CFR 11, 50, 54, 56, 812, ISO 14155: 2020, the ICH Guidelines for GCP, the Declaration of Helsinki (2013) and all other applicable local and national regulations. The study will be registered on www.clinicaltrials.gov.

Acronyms and Definitions

AE	Adverse Event
CRF	Case Report Form
EMR	electronic medical record
EP	electrophysiology
ESI	Event of Special Interest
HU	Healthcare Utilization
ICF	Informed Consent Form
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect

1. BACKGROUND AND RATIONALE

1.1. Overview of Disease

1.1.1. *Arrhythmias*

Cardiac arrhythmias are common and produce considerable morbidity and mortality and are challenging to treat[i]. Symptoms such as dizziness, palpitations, and syncope are frequent complaints encountered by family physicians, internists, and cardiologists. In contrast to these ubiquitous complaints, which are generally benign, sudden cardiac death remains an important public health concern. Statistics from the Centers for Disease Control and Prevention (CDC) have estimated sudden cardiac death rates at more than 600,000 per year. Up to 50% of patients have sudden death as the first manifestation of cardiac disease[ii].

Arrhythmias are one of the most complexes, insufficiently studied, and therefore one of the most urgent problems of modern cardiology. With a wide introduction in the practice of ECG monitoring by Holter as well as the use of individual recorders of electrocardiogram data appeared indicating a much higher frequency of cardiac arrhythmias[iii].

Enormous advances in arrhythmia management have occurred over the 60 years, but important challenges remain. Challenges in diagnosis, detection, and risk-stratification include difficulties in separating benign from high-risk syncope and pinpointing the underlying causes and inadequate identification of sudden-death risk.

As of 2012, approximately 4.3 million Americans experienced some form of cardiac arrhythmia. Annually, 5,750,440 individuals experienced cardiac arrhythmia in the US. Total direct annual healthcare cost of cardiac arrhythmia summed up to $US67.4 billion. Cardiac arrhythmias represent a substantial economic burden in the US, especially for the older adult population[iv].

1.1.2. *Current Treatment Options*

Pharmacologic therapy for arrhythmia is widely used however catheter ablation offers encouraging results in the treatment of most cardiac arrhythmias and is considered as a first line therapy by international guidelines.[v],[vi] Furthermore in the treatment of Atrial Fibrillation (AF) catheter ablation is considered superior regarding freedom of arrhythmia recurrence compared to anti-arrhythmic drug therapy.[vii],[viii],[ix]

Current catheter-based therapy utilizes cardiac 3D mapping and navigation systems that were introduced more than 20 years ago and allow location of the ablation device within a reconstruction of the heart anatomy[x],[xi],[xii],[xiii]. However, technical limitations specific to each available 3D mapping system, such as variability in catheter tip location sensing, alternating location reliability throughout the procedure, and the use of costly specialized catheters and additional hardware (e.g. magnets placed under the operating table, pose limitations of these systems. Furthermore, all available systems provide only an estimate of each individual anatomy, as they do not provide high-quality, real-time

visualization of anatomical structures, but merely a low-resolution reconstruction. In order to obtain more information and a precisely detailed anatomy, time consuming and often costly additional imaging such as fluoroscopy, angiography, echocardiography and even pre-procedural computer tomography (CT) and magnetic resonance imaging (MRI) is required in many cases[xiv].

In conclusion the current procedures are relatively long, considered highly complex and require substantial expertise. In addition specialized catheters and additional hardware is required. The Sponsor has identified these challenges and has developed the KODEX - EPD system to address them successfully.

1.1.3. *Cryoballoon Ablation Therapy and Technology*

Pulmonary vein isolation (PVI), by catheter ablation, represents the current treatment for drug-resistant AF[xv]. Due to its ease of use, fast procedures and durability of lesions in a high percentage of PVs leading to excellent clinical outcome, Cryoballoon Ablation is a recognized ablation method in patients with atrial fibrillation[xvi]. However, cryoballoon ablation requires extensive fluoroscopic guidance to position the balloon catheter at the pulmonary veins often leading to prolonged radiation exposure and possible contract induced kidney injury.

1.2. **KODEX-EPD System**

1.2.1. *Description of the KODEX-EPD System*

The KODEX - EPD system is an open platform that uses any validated EP catheter to create real-time 3D images of the human heart. The KODEX-EPD system takes advantage of the unique dielectric properties of biological tissue by inducing anisotropic electrical fields within the patients´ body and measuring the resultant subtle electrical field differences on the catheter electrodes as they move in the hearts´ chambers. The anisotropic fields are induced by one or multiple sources such as external sensors on the body surface and the diagnostic and/or an ablation catheter. The system receives and analyzes the electrical field transmission and reflection from all catheter electrodes as they are manipulated in the cardiac chambers. Structures such as the endocardial atrial surface, cardiac veins, and heart valves cause marked gradients in the electrical field. This “bending of the electrical field” is sensed by the system and used to calculate the geometric characteristics of the three-dimensional (3D) image. With this technique, the KODEX-EPD System collects anatomic information, without immediate physical surface contact, a few millimeters ahead of the catheter electrodes, resulting in a certain degree of “far-field imaging”. The catheter serves as an internal distance ruler for scaling of the geometry by comparing the known inter electrode spacing versus the voltage difference between the 2 electrodes. The system records a specific set of electrical field descriptors for each specific position of the catheter within the cardiac anatomy and can thereby determine relative positions and distances between locations within the chamber. At each location, the electrical field descriptors that the KODEX-EPD System acquires are used to reconstruct the chamber geometry.[xvii]

1.2.1.1. Study device

The KODEX-EPD system is manufactured by;

Philips Medical Systems Nederland B.V.
Veenpluis 6
5684 PC Best
The Netherlands

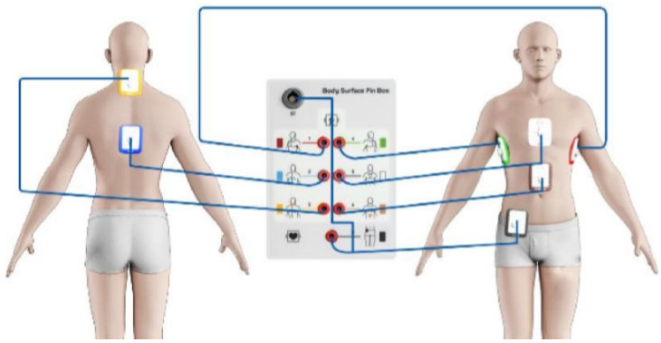
The study device hardware consists of a;

- Processing Unit (version 1.2)
- Workstation
- Body Surface pin box
- Diagnostic Catheter pin box (2x)
- Recording system pin box (2x)
- Foot Pedal

Figure 1: System Overview

The most recent commercialized version of the software will be used for the purpose of this study. Currently this is software version 1.4.8

The KODEX-EPD system is designed to be used with validated commercially available diagnostic and therapeutic catheters. The KODEX-EPD System is supported with dedicated KODEX-EPD sensors and catheters activation keys for RF and Cryo ablation interventions.



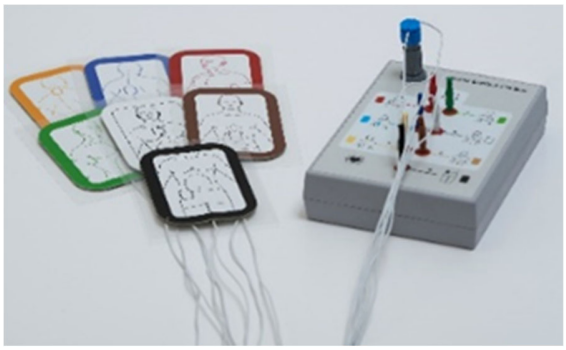


Figure 2: Procedural Disposables

The KODEX - EPD system interfaces with the following commercially available components and devices:

1. **Display:** shows in real-time, and throughout the procedure, the cardiac chamber's geometry and all indwelling catheters.

2. **RF generator:** commercially available RF generators can be connected to the KODEX - EPD system PU, which is then connected to the ablation catheter. The following commercially available RF generators have been tested with the KODEX - EPD system PU:
   - KODEX - EPD RF Ablation System
   - Stockert 70 (Biosense Webster) RF Generator
   - SmartAblate (Biosense Webster) RF Generator
   - Maestro 4000 (Boston Scientific) RF Generator
3. **Standard EP diagnostic and ablation catheters:** for a full list of commercially available compatible catheters, refer to KODEX - EPD system List of Compatible Catheters.
4. **Recording system (includes pacer connection):** commercially available recording systems, such as Prucka CardioLab EP Recording System (General Electric) or LABSYSTEM PRO (Boston Scientific).

1.2.1.2. KODEX-EPD system updates.

The Instructions for use (IFU) will be provided containing the information on the most current software and hardware versions that will be used. Please note that the CIP will not be updated if the hardware/software version is updated unless the update results in;

- an updated clinical workflow described in this CIP;
- an updated benefit-risk analysis;
- an update to the study design;
- an update to the data to be collected;
- any other update that would affect the execution of this clinical investigation.

1.2.2. *Intended Use*

The KODEX-EPD system has received FDA approval and CE mark for creating real-time 3D images of the human heart using validated commercially available diagnostic and therapeutic catheters.
For the purpose of this study we will be using the KODEX-EPD system in its intended use as described in the User Manual

1.2.2.1. Training and Experience

Trained sponsor personnel will be responsible for the set-up of the KODEX-EPD system and will operate the system during the procedure. Physicians completing the EP procedures will have received training on the KODEX-EPD system prior to including the first subject in the study. This training is outside the scope of the study.

1.2.3. *Limitations for use*

There are no special clinical situations that could potentially affect or limit the system performance and accuracy.

1.2.4. *Exposure to Study Device*

The KODEX-EPD System is used to assist the physician during cardiac ablation procedures in patients with a cardiac arrhythmia. The patient will be connected to the KODEX-EPD system via the KODEX-

EPD sensors shown in Figure 2. The duration of exposure to the Study device for both the operator and patient will be the length of the cardiac ablation procedure.

1.3. **Study design justification**

1.3.1. *(Pre)Clinical Studies with the KODEX-EPD System*

The system's measurement and localization capabilities have been validated and the location accuracy and distance score measurements demonstrated that the system is highly accurate, whereas the DURABLE-I clinical study demonstrated safety and efficacy of the KODEX-EPD system. Another study demonstrated that the 3D image quality generated by the KODEX-EPD system is noninferior to CARTO 3 (Biosense Webster) and accurately detects catheter location[xviii]. Clinical data to date has not demonstrated any adverse device effects.

1.3.1.1. Cryo Occlusion feature:

The performance of the Cryo Occlusion feature was validated by means of retrospective analysis of a database of KODEX files from routine cases for which the occlusion status on venography was available as ground truth. For each occlusion event from the database the occlusion status on KODEX was determined with the final version of the KODEX occlusion algorithm and compared against the corresponding occlusion status on venography as ground truth. The accuracy of the Cryo Occlusion feature for the baseline workflow was 92.1%, and for the injection workflow 90.4%, both of which exceed the pre-defined acceptance criteria of ≥ 90%. The clinical acceptability of the workflow of the Cryo Occlusion feature was evaluated by replay of a subset of the KODEX files (n=10) from the database with a final version of KODEX software. During replay of these cases, five clinical specialists filled in a questionnaire in which they each answered questions related to four user requirements of the Cryo Occlusion workflow and provided a score using a 5-point Likert scale. The average scores were 4.0, 4.4, 3.6, and 3.6, and thereby the test was passed because the pre-defined acceptance criteria was ≥3.

1.3.2. *Relevant Literature on the KODEX-EPD System Cryoballoon Occlusion feature*

Several manuscripts on the occlusion feature have been published to date, [xix,xx,xxi,xxii.] reporting that the KODEX-EPD Occlusion feature is safe, feasible, and effective in assessing the degree of PV occlusion during AF cryoablation.

1.3.3. *Study Justification*

Current clinical studies on the KODEX-EPD occlusion feature have reported on the safe and effective use of the system in standard practice. However, the performance of the KODEX-EPD occlusion feature has not been evaluated using a standardized workflow in a blinded setting in a homogenous patient group. Furthermore, in an effort to minimize therapy, a direct comparison between the success of the freeze when initiating therapy based on the occlusion feature vs the assessment of occlusion by fluoroscopy has not been evaluated. The study design indicates a post-market interventional clinical

investigation to evaluate the endpoints of the study. No follow-up is foreseen ensuring a minimal burden to the subjects participating in the study.

2. EXPERIMENTAL PLAN

2.1. Study Objectives

The study objective is to evaluate the performance of the KODEX-EPD PV occlusion feature as compared to conventional venographic method of fluoroscopy with contrast dye in cryoballoon procedures that is used to guide the procedure. Performance will be calculated in terms of accuracy, sensitivity, specificity and positive and negative predictive values. In the blinded arm of this 2-armed study, the operator will be blinded for the PV occlusion data on the KODEX-EPD system, and this data will not be used for clinical guidance. In the KODEX guided arm the operator will use the KODEX-EPD system occlusion data to guide the procedure.

2.2. Study Design

2.2.1. *Study Schematic*

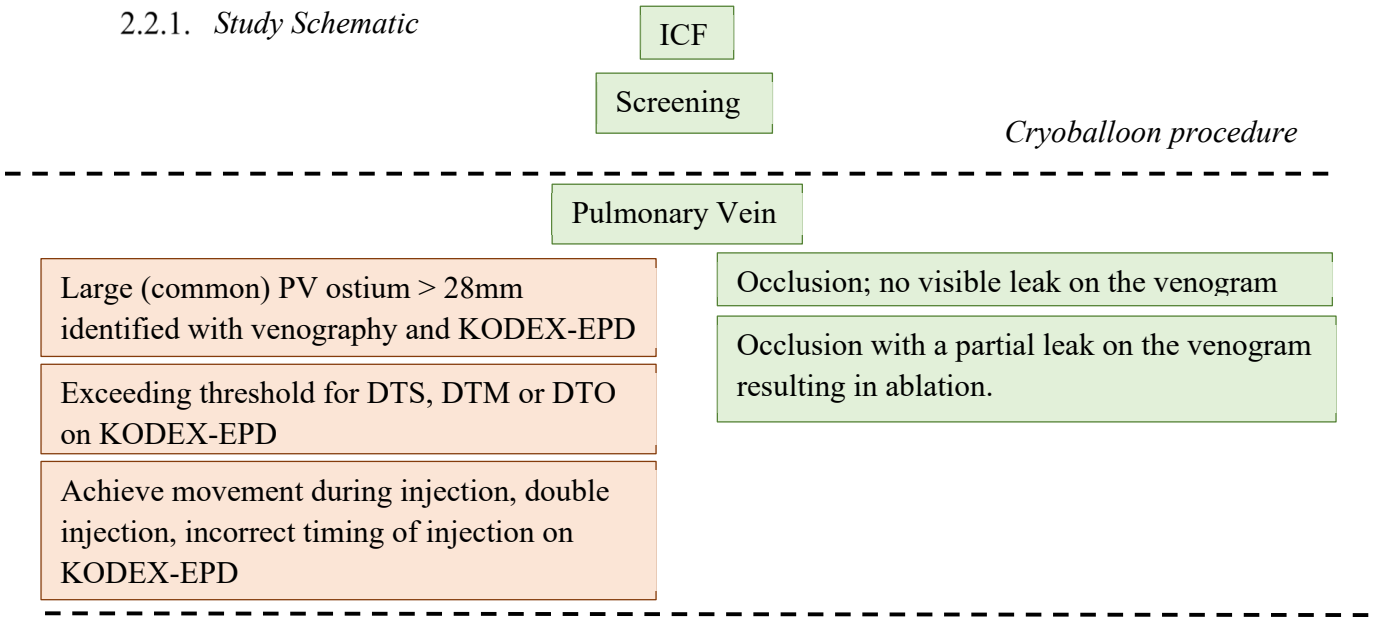


Figure 3; Study Schematic

The Cryoballoon procedure consists of the isolation and ablation of the pulmonary veins (PVs). The number of PVs and occlusion tests per PV depends on several factors including patient anatomy. Therefore, data from the KODEX-EPD PV Occlusion feature will be evaluated as a separate set of data for each occlusion test and for each pulmonary vein. Data from a PVI where the diameter of the (common) PV ostium > 28mm, or when the threshold for Distance to Shadow (DTS), Distance to Mesh (DTM) or Distance to Ostium (DTO) is exceeded, or when the Achieve catheter is moving during the

injection, there is a double injection or an incorrect timing of the injection, will not be included in the primary endpoint analysis.

2.2.2. *Primary Endpoints*

1. The accuracy, sensitivity, specificity and positive and negative predictive values of the KODEX-EPD PV occlusion feature as compared to conventional angiographic method of fluoroscopy with contrast dye that will be used to guide the procedure.
2. The success of the freeze when freeze is initiated based on the assessment of the KODEX-EPD PV occlusion feature as compared to the success of the freeze when freeze is initiated based on the assessment with fluoroscopy and contrast dye.

2.2.3. *Secondary and Exploratory Endpoints*

Procedure data collection:

- KODEX-EPD data collection
- Fluoroscopy system data collection
- Fluoroscopy time
- Fluoroscopy dose
- Number of contrast dye injections
- Contrast dye volume
- Time to isolation (TTI)/Success of Isolation
- Number of ablations per vein
- Procedure time (skin to skin)

2.2.4. *Study Duration*

The study enrolment is expected to take 1.5 years. The study has no F/Up therefore the total duration is expected to be 1.5 years.

2.3. **Study Centers**

In total Two (2) centers; Johns Hopkins University in Baltimore, USA and UZ Brussel in Brussel, Belgium will participate in the study

2.4. **Number of patients**

A maximum of 20 patients per center will be included in the blinded to KODEX arm of the study. An additional 25 patients will be included at UZ Brussel in the KODEX guided arm of the study.

2.5. **Subject Selection and Enrollment**

2.5.1. *Study Population and Eligibility*

Subjects will undergo baseline evaluation to determine eligibility for the study.

After being informed of the nature of the study, the subject will sign a written informed consent form (ICF) that has been approved by the IRB/EC of the clinical site and by the Sponsor. Subjects will be considered for the study if they meet the specific inclusion/exclusion criteria. The criteria for enrollment must be followed explicitly.

2.5.2. *Inclusion Criteria*

1. Subject must be aged >18 years.
2. Subject must have signed a written Informed Consent form to participate in the study, prior to any study related procedures.
3. Subject must be willing to comply with the protocol requirements.
4. Subject receives a de novo ablation procedure for treatment of atrial fibrillation.

2.5.3. *Exclusion Criteria*

1. Pregnant women.

2.5.4. *Withdrawal*

Every effort should be made to retain subject enrolment for the duration of the study. During the informed consent process subjects should be fully informed of the data collection requirements and duration and should only be enrolled if willing to fully participate in it. All subjects enrolled in the clinical study must be accounted for and documented. Reasons for withdrawal may include;

- Physician discretion
- Subject choice to retire consent, loss to Follow up, or death.

In the event that the subject withdraws from the study every effort should be made to obtain full information on any on-going adverse events.

The reason for withdrawal must be recorded in the End of Study (EoS) CRF and in the patient file. All open adverse events should be closed or documented as ongoing. Data collected up to the point of subject withdrawal may be used, unless any local regulations prohibits the use of the data.

2.6. **Study Procedures**

2.6.1. *Screening and Informed Consent*

Patients who may be eligible for enrollment will go through the informed consent process. At the screening visit, subjects will be approached to obtain written informed consent prior to any study specific procedures being performed. The purpose of the study and the benefits and risks of the procedures will be explained to the subject and the consent process must be documented accordingly in the medical record. Subjects who agree to study participation must sign an approved ICF. Subjects will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Subjects will be given the opportunity to ask questions so that

they are adequately informed about the research. A copy of the signed informed consent must be provided to the subject and the informed consent process will be documented in source documents. Subjects are considered enrolled once their informed consent has been correctly documented.

If new information becomes available that may affect a subject's decision to continue to take part in the study, this information will be discussed with the subject.

Subjects who are unable or unwilling to provide written informed consent should not be included in the investigation.

The following assessments/procedures will be performed during the screening, following the institutions' standard protocols:

- Demographics
- Medical history
- Physical examinations
- Concomitant medications
- Presence/history of atrial fibrillation
- Previous and current treatments of atrial fibrillation

2.6.2. *Intervention*

Patient management and treatment decisions are at the discretion of the care team per routine clinical practice. The KODEX-EPD system is an open-platform system however all catheters/leads used during the intervention need to be calibrated prior to the intervention.

2.6.2.1. Clinical Workflow

1) Advance the Achieve spiral mapping catheter (Achieve) to the Left Atrium (LA).
2) Image the LA with the Achieve by maneuvering the catheter around the LA under different angles.
3) Inflate the Cryoballoon (CB) and advance CB to occlude the ostium, make sure the location of the Achieve is maximal 15 mm distal to the CB. Hold this location for 5 seconds.
    - KODEX-EPD System will obtain a "shadow" of the Achieve at the current location this will take approximately 2 seconds.

Please note that there are 2 types of notifications on the KODEX-EPD system that can be shown when obtaining the 'shadow';
- ***DTM; When the distance between the Achieve and the Mesh is > 10mm***
- ***DTO; When the distance between the Achieve and the Ostium is > 35mm***

It is recommended to reposition the catheter and acquire a new shadow

4) Verify occlusion on fluoroscopy (in the blinded arm) or KODEX(in the KODEX guided arm) by selective contrast injection while simultaneously stepping on the KODEX-EPD System's foot pedal/or the injection button in the KODEX-EPD system is pressed to start the occlusion

assessment with the KODEX-EPD System. The occlusion assessment will take approximately 12 seconds. After which the physician should decide to;

- Proceed with CB ablation and move to next PV
- Reposition CB and repeat step 4.

Please note that for a successful occlusion assessment on the KODEX-EPD system it is important that;

- ***The there is no DTM, DTO or DTS (When the distance between the Achieve and the Shadow is > 10mm) notification on the KODEX-EPD system***
- ***The injection on the KODEX-EPD system is synced with the actual injection***
- ***The Injection is done with one shot.***

If occlusion is not indicated when assessing occlusion in the KODEX guided arm it is recommended to reposition the CB and re-assess the occlusion with KODEX. In total 3 consecutive attempts should be made to obtain occlusion on KODEX.

It is recommended to use an auto-injector where 6cc is injected at 2.5ml/sec and the dye/saline ratio is between 50/50 to 100/0.
If a manual syringe is used the injection should be swiftly and the dye/saline ratio needs to be between 70/30 to 100/0. The amount of injection is at the physician's discretion.

Considerations for the use of contrast in this workflow are the following;

- The contrast injection induces a significant local dielectric change and impacts some/all readings off the Achieve electrodes.
- The contrast needs to reach and embed the Achieve electrodes.
- Monitor no movement during injection.
- The Achieve's proximity to the CB will impact the results.

2.6.2.2. Data Collection

The following data will be collected during the intervention:

- KODEX-EPD data collection
- Fluoroscopy system data collection
- Fluoroscopy time
- Fluoroscopy dose
- Number of contrast dye injections
- Contrast dye volume
- Information on durability of the PV isolation.

- Time to isolation (TTI) – if possible
- Number of ablations per vein
- Procedure time (skin to skin)
- cineloops of procedural images
- Cryoconsole freeze data
- Safety Events

2.6.3. *Follow up*

This is an acute study and there is no follow-up foreseen.

2.6.4. *Discharge & End of Study*

The End of Study (EoS) is defined as after patient's discharge. The following data will be collected during the Discharge/EoS visit;

- Vital signs
- Concomitant medication
- Safety Events

2.6.5. *After End of Study*

After the study participation has ended the subjects will be followed up at the discretion of the investigator in accordance with the standard of care. No additional follow up is intended after Subjects' participation in the study has ended.

Subject data may be collected after the subjects' end of study. Following the FDA guidance; all AEs and non-study related SAEs should be followed up until they have resolved or stabilized or until 30 days after participants' EoS. All other SAEs should be followed until resolution or until the condition has stabilized with no further change expected.

Data collected for the purpose of this study may be used for future clinical research in the area of cardiac ablations.

2.6.6. *Schedule of Assessments*

Table 1; Schedule of Assessments

	Screening	Intervention	Discharge/EoS
Visit window	**≤ - 1 month**	**-**	**-**
Informed consent	x		
Medical History	x		
Physical Examinations	x		
Vital Signs	x	x	x
Demographics	x		
Incl./Excl. Criteria	x		

TEE	x[1]	x[2]	
12-Lead ECG	x[1]	x[2]	
Fluoroscopy time and dose		x[3]	
Contrast dye # of injections and volume		x[3]	
TTI		x	
# of Ablations per PV		x	
Procedure time		x	
cineloops of procedural images		x	
Cryoconsole freeze data		x	
Concomitant Medications	x	x	x
(S)AE reporting	x	x	x

[1] Only collect data when assessment is done per standard of care within 1 months of screening. Assessment doesn't require to be done for the purpose of the study.

[2] Only collect data when assessment is done per standard of care. Assessment doesn't require to be done for the purpose of the study.

[3] Data from 2 intervals;

1. start of procedure – transseptal puncture
2. successful transseptal puncture – isolation

2.6.7. *Standardization of Study Procedures*

2.6.7.1. Measurements of Vital Signs

Blood Pressure (BP) and Heart Rate (HR) measurements should be determined after the subject has been seated for at least 5 minutes. BP should be measured on both arms and the arm with the highest systolic reading at screening should be used for BP determination throughout the study. The subject's pulse should be measured for 30 seconds and the number should be multiplied by 2 to obtain HR.

2.6.7.2. Concomitant Medication

Targeted concomitant therapy and medications will be recorded on the CRF. The following groups of concomitant medications will be recorded;

- Anticoagulants
- Cardiovascular medications
- Antiarrhythmic medications/substances

2.6.7.3. Procedural Images

Cineloops of procedural images are to be created starting just prior to contrast injection for fluoroscopic verification of occlusion for a duration of 5 seconds and should include one respiratory cycle. A visual assessment of the occlusion should be made by the physician at that time and documented in the procedural notes. The images will be collected and reviewed for an independent assessment.

3. RISK/BENEFIT ANALYSIS

3.1. Potential Risk to the Subject

The KODEX-EPD system used in this study is cleared for commercial use by the FDA and is CE-certified; therefore, the use described in this protocol constitutes a standard clinical use. Information related to contraindications, adverse effects, warnings and precautions are included in the device instructions for use. Patients enrolled do not bear additional clinical risk by participating in this study.

The sponsor has taken all the necessary precautions and applied the required mitigations, as described in the risk analysis document, in order to make even the rarest risk become virtually impossible.

Nevertheless, potential complications that could be related to the system include, but are not limited, to the following anticipated AEs:

- Skin allergy due to body external patches
- Secondary transient hyper-hydrosis due to local skin irritation
- Local superficial burns (return electrode)
- Hampering the quality of recorded intra-cardiac electrical signals that are being transferred to the recording system through the KODEX-EPD system (noise introduction)
- Decreasing the power output of the RF generator; thereby potentially affecting the generated ablation lesions
- Incorrect reading of the catheter's tip electrode impedance at rest or during ablation as presented on the RF generator front panel
- Incorrect reading and presentation of the tip electrode temperature as read by the RF generator
- Incidental electrocution

3.2. Potential Benefits to the Subject

No direct benefits to the patient are expected.

3.3. Benefit-Risk Rationale

The KODEX-EPD and accessories used for the PROOF Study will be commercially available and are considered to be SOC for subjects indicated for cryoballoon PVI Procedures. The risks involved with subject participation in this study are essentially the same as those for subjects not participating in the study.

4. SAFETY DATA COLLECTION, RECORDING AND REPORTING

Adverse events and serious adverse events as defined below will be captured once the patient has signed the informed consent form. However, the primary endpoint analysis will count only adverse events for patients that the KODEX-EPD system has been used during the treatment procedure.

4.1. Definitions

4.1.1. *Adverse Events (AE)*

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the KODEX-EPD system or accessories and whether anticipated or unanticipated. This definition includes events related to the investigational medical device or the comparator.
Additionally, this definition includes events related to the procedures involved.
For users or other persons, this definition is restricted to events related to the use of the KODEX-EPD system or accessories or comparators.
This definition includes events related to the procedures involved.

4.1.1. *Adverse Device Effect (ADE)*

An adverse event related to the use of KODEX-EPD System or accessories or the comparator.
This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the KODEX-EPD System.
This definition includes any event resulting from use error or from intentional misuse of the KODEX-EPD System.

4.1.2. *Serious Adverse Event (SAE)*

The Investigator must decide whether each event meets the definition of a “serious” adverse event (SAE). SAE is defined as any adverse event that:

- Led to death,
- Led to a serious deterioration in health of the subject, users or other persons that either:
  - Resulted in a life-threatening illness or injury, or
  - Resulted in a permanent impairment of a body structure or a body function including chronic diseases, or
  - Required in-patient hospitalization or prolongation of existing hospitalization, or
  - Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

NOTE: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a SAE.

4.1.3. *Serious Adverse Device Effect (SADE)*

An adverse device effect (section 4.1.1) that has resulted in any of the consequences characteristic of a serious adverse event as mentioned in section 4.1.2.

4.1.4. *Unanticipated Serious Adverse Device Event (USADE)*

An unanticipated serious adverse device event (USADE) is defined as any 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.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

4.1.5. *Device Deficiencies*

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling. This definition includes device deficiencies related to the KODEX-EPD System or accessories or the comparator.
All KODEX-EPD system device deficiencies will be documented in the CRF. Devices that malfunction during the procedure will be analyzed by the sponsor, after appropriate decontamination per hospital guidelines.
Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate CRF.

4.1.5.1.Malfunction

A malfunction is a failure of the KODEX-EPD System or accessories or the comparator to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

4.1.5.2.Use Error

A use error can be defined as a user action or lack of user action while using the KODEX-EPD System or comparator that leads to a different result than that intended by the manufacturer or expected by the user. This includes the ability by the user to complete a task.

NOTE: A malfunction of a medical device that causes an unexpected result is not considered a use error, nor does an unexpected physiological response of the patient.

4.2. **Adverse Event Classification**

4.2.1. *Severity Classification*

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)
Severe	Incapacitating, with an inability to perform ADL

4.2.2. *Relationship Classification*

The investigator's assessment of an AE/SAE's relationship to study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE/SAE, the event should be reported. The relationship or association of the study device in causing or contributing to the AE/SAE will be characterized as one of the following:

- ***Not Related***: No relationship between the AE and the administration of study treatment and a known relationship to other etiologies such as concomitant medications, or subject's clinical state.
- ***Possibly Related***: An AE that follows a reasonable temporal sequence from the use of the study device/procedure and follows a known response pattern to the study device/procedure but could have been produced by the participant's clinical state or by other therapies.
- ***Probably related***: An AE that follows a reasonable temporal sequence from the use of the study device/procedure; follows a known response pattern to the study device/procedure; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.
- ***Related***: An AE that follows a plausible temporal sequence fromthe use of the study device/procedure; follows a known response pattern to the study device/procedure. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- ***Unknown***; Given the information available, sequence and timing of events, it is unknown or impossible to determine the relationship between the AE and the study device/procedure.

4.2.3. *Outcome Classification*

Outcome of the event will be defined according to the following:

- ***Resolved****:* The event has fully resolved at the end of the study.
- ***Resolved with sequelae***: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.
- ***Continuing****:* The event is ongoing at the end of the study.
- ***Death****:* This event is determined to be the cause of death.

4.3. **Reporting**

4.3.1. *Reporting of AEs and ADEs*

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event e-CRF and followed as appropriate.
For the purpose of this study we will selectively collect AEs; meaning that only AEs directly or indirectly related to the EP intervention and/or any cardiac arrhythmia will be collected. Selective AE reporting is in line with the FDA's approach to a safety assessment that is focused on information that is useful and adds to current knowledge.
As far as possible, each adverse event will also be described by:

- its duration (start and end dates)
- the severity
- its relationship to the study device (unrelated/possible/probable)
- the action(s) taken

4.3.2. *Reporting of SAEs SADEs and USADEs*

For the purpose of this study and based on the definitions above and the requirements of the European authorities the following events are considered reportable events in accordance with Annex 7, section 2.3.5 and 93/42/EEC respectively:

- Any SAE whether or not considered as related to study device
- Any KODEX-EPD system deficiency that might have led to a SAE if:
    a. Suitable action had not been taken, or
    b. Intervention had not been made, or
    c. If circumstances had been less fortunate
- New findings /updates in relation to already reported events

All USADEs, SAEs and SADEs, will be reported on specific forms, if applicable, and forwarded to the Sponsor within 24 hours of first awareness of the event. The Investigator is also responsible for complying with the applicable local requirements related to adverse event reporting.
The investigator must complete the appropriate event report form in English, assess the relationship to study device/procedure and e-mail the completed form to the Sponsor at:
EPDEventReporting@philips.com.
Follow-up information about previously reported USADEs, SAEs and SADEs must also be reported to the Sponsor within 24-hours of receipt. The Follow up information should be reported on a new event report form by referring to the subject and event number. Only new/updated information needs to be entered on the event report form.

Original and the duplicate copies of the event report forms must be kept at the study site. The monitor will review and collect copies of the completed event report forms and related documentation.

If the SAE has not been previously documented (new occurrence) and it is thought to be related to study device, Sponsor's Medical Expert may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same device that this serious adverse event has been reported.

5. STATISTICAL CONSIDERATION

5.1. **Study Endpoints**

5.1.1. *Primary Endpoints*

1. The accuracy, sensitivity, specificity and positive and negative predictive values of the KODEX-EPD PV occlusion feature as compared to conventional venographic method of fluoroscopy with contrast dye that will be used to guide the procedure.
2. The success of the freeze when freeze is initiated based on the assessment of the KODEX-EPD PV occlusion feature as compared to the success of the freeze when freeze is initiated based on the assessment with fluoroscopy and contrast dye.

5.1.2. *Secondary Endpoints*

- KODEX-EPD data collection
- Fluoroscopy system data collection
- Fluoroscopy time
- Fluoroscopy dose
- Number of contrast dye injections
- Contrast dye volume
- Time to isolation (TTI)
- Number of ablations per vein
- Procedure time (skin to skin)

5.2. **Analysis Sets**

The Primary Analysis Set (PAS) includes all successful occlusion tests. Successful is defined as a test for which;

- procedural data e.g.: KOPDEX-EPD system data, venograms, and notes are obtained.
- Presence of DTS, DTM or DTO notifications were documented before obtaining the shadow.

This analysis set will be used for the primary endpoint analysis.

The Secondary Analysis Set (SAS) includes all PVIs and ablations done. This analysis set will be used for the analysis of the secondary endpoints.
The ITT (intend to treat) PVs will be used as a secondary analysis of the secondary endpoints.

5.3. **Sample Size Considerations**

The sample size for the 1st primary endpoint was determined at 120 resulting in approximately 30 subjects to be enrolled in the blinded arm.
The sample size for the 2nd primary endpoint was estimated using the One-Sided Lower-Limit Confidence Intervals for One Proportion approach. Expecting a proportion of 80% with a lower bound of the 95% confidence interval of about 70% the sample size is estimated to be 87.

A sample size of 87 would require approximately 22 subjects to be enrolled in the KODEX guided arm.

5.4. **Statistical Analysis**

5.4.1. *General Approach/Considerations*

Statistical analyses in this data collection study will be descriptive in nature. No statistical inference is planned. Subject disposition, demographics and baseline characteristics will be summarized. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Interim and final analyses will be based on data collected from this study. There will be no imputation for missing data.

5.4.2. *Analysis of Key Study Endpoints*

5.4.2.1. Primary Endpoint Analyses

Results will be summarized by occlusion test, by PV and by patient.

5.4.2.2. Secondary Endpoint Analyses

Results will be summarized by PV and by patient.

5.4.2.3. Exploratory Endpoint Analyses

Results will be summarized by occlusion test, by PV and by patient.

5.5. **Data justification**

Systemic error/bias will be minimized by having operators select subjects from their general patient population. Before enrolling subjects, sites/operators will be trained on the study protocol to ensure consistency across sites/operators. Subjects will be equally distributed over the 2 sites in the blinded arm of the study.

5.5.1. *Missing Data*

No imputations for missing data will be made. This is an acute study with no F/Up foreseen.

5.5.2. *Deviations*

Any changes to the planned statistical analyses made will be documented in a separate Statistical Analysis Plan. Changes from the planned statistical methods will be documented in the clinical study report along with a reason for the deviation. Post-hoc analyses may be conducted according to the existing data collected, if necessary

6. STUDY CONDUCT

6.1. **Statement of Compliance**

This study will be conducted in accordance with ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice, and the relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations including but not limited to EU-MDR. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board (IRB)/Ethics Committee (EC) and/or regulatory authority has been obtained, if appropriate.

The Investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator must notify the IRB/EC of deviations from the protocol or SAEs and USADEs occurring at the site in accordance with local procedures. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

The Investigator is responsible for obtaining annual IRB/EC approval and renewal throughout the duration of the study where applicable. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

Insurance shall be provided for the subjects participating in this clinical trial according to local law.

The clinical study will be sponsored by EPD Solutions whereas the financial compensation for the investigator/site is defined as an Exhibit to the clinical trial agreement.

6.2. **Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include but are not limited to: medical records, clinic and office charts, x-rays, laboratory notes, study specific worksheets, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, subject files, and records kept at the pharmacy and at the laboratories involved in the clinical trial.

Regulations require that the Investigator maintain information in the subjects' medical/hospital records that corroborate data collected for the study. In order to comply with these regulatory requirements, at a minimum, the following is a list of information that should be maintained:

- Medical history/general physical condition of the subject before involvement in the study of a sufficient nature to verify the protocol eligibility criteria
- Dated and signed study/progress notes on the date of entry into the study documenting the following:
  - The general health of the subject;
  - The discussion of the study risks and benefits with the subject;
  - Completion of the informed consent process;
  - A statement that the subject has reviewed, signed, and received a copy of the Subject Informed Consent Form;
  - Adverse Events reported and their continuation or resolution, including supporting documents such as discharge summaries, X-ray reports, and other test reports;
  - Subject's general health and medical condition upon completion of, or withdrawal from, the study.

Subject confidentiality will be maintained throughout the clinical study in a manner that assures data can be traced back to the source documents. Additionally, subject information will be managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In addition, all personal data will be handled in accordance with the EU directive e95/46/EC and as of 25 May 2018 in accordance with the GDPR. All data will be de-identified at each site before being entered into EDC. Only the investigator and site coordinator will have access to the de-identified data. The Informed Consent Form must include information letting the subject know:

- What protected health information (PHI) will be collected during the study;
- Who will have access to that information;
- Who will use or disclose that information;
- The rights of the research subject to revoke their authorization for use of their PHI.

In the event that the subject revokes authorization, the investigator retains the ability to use all information collected prior to the revocation. The Investigator should attempt to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

6.3. **Data Handling and Record Keeping**

This study will be performed using an electronic data capture (EDC) system. The e-CRF will be used for data review, data cleaning and issuing and resolving queries. This e-CRF is a web-based e-CRF which is password protected and is 21 CFR part 11 compliant. The investigator and study site staff will receive training and support on the use of the EDC system and will be granted specific user privileges. All CRF data are to be completed by the investigator, study coordinator, or other designated site

personnel. The investigator will perform a final review and sign-off at designated times (e.g. study exit).

Site coordinators will be trained to enter data into a web-based electronic data capture system designed for this study and for maintaining its data. Source data verification between the CRF and the subject's medical records will be completed by a monitor during onsite visits. Monitoring of the data will be completed during ongoing remote data reviews. The clinical database will be a closed system, allowing for tracking all the data elements and any changes made.

Raw data that is collected from the KODEX-EPD System and other image data collected through modalities used for during the standard of care intervention will be de-identified and stored in a secured location.

Sponsor will provide the investigational site with supplies for setting up the study files. Study documents must be maintained by the Investigator and Sponsor for the duration of the trial and for a period of at least 15 years after the trial has been formally closed.

6.3.1. *Device Accountability*

Although the study does not foresee the provision of study devices, the site will be responsible to ensure that all study supplies and patient records are kept in a secure place.
No accountability records for the KODEX EPD system and sensors must be maintained when these are purchased through regular commercial channels. Device accountability is required to be maintained if the system and/or sensors are provided for the sole purpose of the study. If device accountability is required the principal investigator shall keep records documenting the receipt, use, return and disposal of the study device, including date of receipt, identification of each study device, the expiry date, the date of use, subject identification, the date of return of unused, expired or malfunctioning investigational devices and date on which the investigational was returned.

6.4. **Investigator Responsibilities**

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other

relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to the sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a USADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a USADE, if required by the national regulations or this protocol or by the IRB/EC, and supply the sponsor with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

6.4.1. *Delegation of Responsibility*

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

6.4.2. *Protocol Deviations*

An Investigator must not make any changes or deviate from this CIP except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor within 14 days using the appropriate CRF. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the sponsor or its representatives.

6.5. **Sponsor Responsibilities**

6.5.1. *Confidentiality*

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential by the Sponsor. Only authorized Sponsor personnel or a Sponsor representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by the Sponsor for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

The Sponsor will keep subjects' health information confidential in accordance with all applicable laws and regulations. The Sponsor may use subjects' health information to conduct this study, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical

research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

6.5.2. *Monitoring*

Monitoring (on-site and remote) will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original or electronic source documents by Sponsor's personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by the Sponsor or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

6.5.3. *Insurance*

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study related illness/injury in accordance with the information provided in the Insurance section of the Informed Consent document.

6.5.1. *Amendments to the CIP*

Non-significant changes of the CIP may be included (minor logistical or administrative changes not effecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints), without prior approval. Significant changes (such as device modifications, study procedures) shall be discussed with the coordinating investigators and principal investigator prior approval. All changes will be documented with a justification and described in the CIP. Changes shall be authorized by the IRB/EC and if applicable the Competent Authority before implementation. Exempt from this requirement are measures which have to be taken immediately in order to protect the participants.

7. PUBLICATIONS

It is Sponsor's policy to publish the results of its Clinical Studies.

This study will be registered on clinicaltrial.gov before first enrollment.

The publication of the common database will be under the direction of EPD. Publication of the complete data set will not be allowed unless approved by the sponsor.

Individual investigators may publish their own data sets upon sponsor approval, if it contains data that is unique to that center. Otherwise, this will not be allowed before the common data sets have been published.

All publications will be reviewed by the Sponsor in order to assure that no confidential information is disclosed. Such confidential information will be published only after the Sponsor's Intellectual Property has been protected.

8. GENERAL INFORMATION

8.1. Study Contact Information

Questions regarding this study should be directed to the clinical study manager.

Marieke van Bussel
Veenpluis 6 Building QP
5684 PC Best, The Netherlands
Tel +31 (0)6 39267909
Marieke.van.Bussel@philips.com

8.2. Retention of Records

All source documents and CRFs will be kept for a period of 2 years after the later of the following dates: the date at which the study is terminated or completed or; the date that the records are no longer required for supporting marketing applications.

8.3. Study Completion/Termination or Suspension of the Study

There are no provisions or interim analyses planned that can result in an early termination of the study. The principal investigator, IRB/EC, or regulatory authority may suspend or prematurely terminate participation in the clinical study at the investigation sites for which they are responsible.

Any signs of unknown or increased risks for the subjects will be discussed by the sponsor and investigator to assess the impact on the subjects and clinical investigation. If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the IRB/EC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed.

The sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the IRB/EC or the regulatory authority.

8.3.1. *Reporting Timelines*

A final report shall be provided to all reviewing IRBs/ECs, and the participating Investigators within 6 months after termination/completion.

8.3.2. *Subject Follow up*

Following an early termination, suspension or study completion, patients who are already treated and not discharged will be followed up for adverse events till discharge from hospital. Patients who are already discharged from the hospital will be followed up as per standard of care in the hospital, outside the study.

In addition, all AEs and non-study related SAEs should be followed up until they have resolved or stabilized or until 30 days after participants' EoS. All other SAEs should be followed until resolution or until the condition has stabilized with no further change expected.

8.3.3. *Blinding*

The blind of this investigation will not be broken as the blinding in this study is not of influence on the treatment, the risks of the study device or the benefit risk ratio to the patient.

9. REFERENCES

[i] Stanley Nattel, j. a. (december 2014). New directions in cardiac arrhythmia management: present challenges and future solutions. 30(12), s420–s430.

[ii] http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/cardiac-arrhythmias/ retrieved from clevelandclinicmeded.

[iii] Zatonskaya e.v., m. g. (2017). The prevalence and clinical significance of cardiac arrhythmias. . rational pharmacotherapy in cardiology., 13(3), 403-408

[iv] Tang dh, g. a. (2014 , feb). Economic burden and disparities in healthcare resource use among adult patients with cardiac arrhythmia. appl health econ health policy. , 12(1), 59-71.

[v] Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Rev Esp Cardiol (Engl Ed). 2016;69(2):176.

[vi] Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart rhythm : the official journal of the Heart Rhythm Society. 2016;13(4):e136-221.

[vii] Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circulation Arrhythmia and electrophysiology. 2009;2(4):349-61.

[viii] Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. Jama. 2010;303(4):333-40.

[ix] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology. 2014;64(21):e1-76.

[x] Kuck KH, Ernst S, Cappato R, Braun E, Lang M, Ben-Haim SA, et al. Nonfluoroscopic endocardial catheter mapping of atrial fibrillation. Journal of cardiovascular electrophysiology. 1998;9(8 Suppl):S57-62.

[xi] Ben-Haim SA, Osadchy D, Schuster I, Gepstein L, Hayam G, Josephson ME. Nonfluoroscopic, in vivo navigation and mapping technology. Nat Med. 1996;2(12):1393-5.

[xii] Stevenson WG, Delacretaz E, Friedman PL, Ellison KE. Identification and ablation of macroreentrant ventricular tachycardia with the CARTO electroanatomical mapping system. Pacing and clinical electrophysiology : PACE. 1998;21(7):1448-56.

[xiii] Gepstein L, Hayam G, Ben-Haim SA. A novel method for nonfluoroscopic catheter-based electroanatomical mapping of the heart. In vitro and in vivo accuracy results. Circulation. 1997;95(6):1611-22.

[xiv] Maurer T, Kuck KH, First clinical experience in high resolution imaging of cardiac anatomy using the novel wide band magneto-electric mapping system KODEX.

[xv] Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. [Internet]. 1998;339:659–666.

[xvi] Osório et. al. Recent advances in cryoballoon ablation for atrial fibrillation. Expert Rev. of Med. Devices 2019;16;9:799-808. DOI: 10.1080/17434440.2019.1653181

[xvii] Maurer T, et. Al. High-Resolution Imaging of LA Anatomy Using a Novel Wide-Band Dielectric Mapping System. JACC Clin. EP. DOI: 10.1016/j.jacep.2019.06.020

[xviii] Romanov et. al. High-resolution, real-time, and nonfluoroscopic 3-dimensional cardiac imaging and catheter navigation in humans using a novel dielectric-based system. Heart Rhythm 2019;16;12 1890-1891.

[xix] Cauti, F. M., Rossi, P., Iaia, L., Polselli, M., Pecere, A., & Bianchi, S. (2021). Accuracy comparison of the new and previous Kodex occlusion tool software versions to assess pulmonary vein occlusion in atrial fibrillation cryoablation. European Heart Journal, 42(Supplement_1). https://doi.org/10.1093/eurheartj/ehab724.0386

[xx] Cauti, F. M., Solimene, F., Stabile, G., Polselli, M., Schillaci, V., Arestia, A., Shopova, G., Iaia, L., Giannitti, C. M., Rossi, P., & Bianchi, S. (2021). Occlusion tool software for pulmonary vein occlusion verification in atrial fibrillation cryoballoon ablation. Pacing and Clinical Electrophysiology: PACE, 44(1), 63–70. https://doi.org/10.1111/pace.14130

[xxi] Rillig, A., Rottner, L., Nodorp, M., Lin, T., Weimann, J., Münkler, P., Dinshaw, L., Schleberger, R., Lemoine, M. D., Nies, M., Risius, T., Blankenberg, S., Kirchhof, P., Meyer, C., Reissmann, B., & Metzner, A. (2020). Novel Wide-Band Dielectric Imaging System and Occlusion Tool to Guide Cryoballoon-Based Pulmonary Vein Isolation: Feasibility and First Insights. Circulation. Arrhythmia and Electrophysiology, 13(12), e009219. https://doi.org/10.1161/CIRCEP.120.009219

[xxii] Rottner, L., Sinning, C., Reissmann, B., Schleberger, R., Dinshaw, L., Münkler, P., Meyer, C., Blankenberg, S., Rillig, A., & Metzner, A. (2020). Wide-Band Dielectric Imaging and the Novel Cryoballoon-Occlusion Tool to Guide Cryoballoon-Based Pulmonary Vein Isolation. Circulation. Arrhythmia and Electrophysiology, 13(8), e008507. https://doi.org/10.1161/CIRCEP.120.008507