Clinical Investigational Plan for the
WAVECREST Post Market Clinical Follow-Up (PMCF) Study
CHX_IP015

Study Title: WAVECREST PMCF Study

A prospective, multicenter, non-randomized, post-market clinical follow-up study to confirm safety and performance of the Coherex WaveCrest® Left Atrial Appendage Occlusion System in current medical practice in patients with non-valvular atrial fibrillation

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WAVECREST Post Market Clinical Follow-Up Study

CHX_IP015

Study Title	WAVECREST PMCF Study
Device Name	Coherex WaveCrest® LAA Occlusion System
Device Number	CE Mark Number 0123
Clinical Investigational Plan Number	CHX_IP015
Revision Number	Rev D, including administrative changes #1 and #2
Date	17/Jul/2018
Study Oversight	PPD
Sponsor	Coherex Medical, Inc. 3598 West 1820 South Salt Lake City, UT 84104 USA

INVESTIGATOR SIGNATURE PAGE

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A prospective, multicenter, non-randomized, post-market clinical follow-up study to confirm safety and performance of the Coherex WaveCrest® Left Atrial Appendage Occlusion System in current medical practice in patients with non-valvular atrial fibrillation

Sponsored by: Coherex Medical, Inc.

Document Type	Revision	Protocol/Exhibit Effective Date
Administrative	#1	February 22, 2018
Administrative	#2	July 17, 2018
Protocol	D	July 17, 2018

I, the Undersigned,

Name: _____

Title: _____

Address: _____

_____

_____

acting as an Investigator in the above-mentioned study, undertake to perform the study in due compliance with the present protocol and with all applicable Regulatory, Ethical and Good Clinical Practices requirements, including but not restricted to the latest version of the Declaration of Helsinki, Medical Device Directive (93/42/EEC) and EN-ISO 14155.

No study-specific tests or procedures will be undertaken prior to Ethics Committee approval of the research and individual patient signature of an informed consent to participate in the study. Use of the device will be in full compliance with this Clinical Investigational Plan and product Instructions for Use. Reporting of adverse events and vigilance data will be performed in compliance with local regulatory requirements.

Signature: _____ Date: _____

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1.0 Summary

Study Title	WAVECREST PMCF Study
Name of Device	Coherex WaveCrest® Left Atrial Appendage Occlusion System
CE Mark Number	CE 0123 issued August 2013
Purpose	To confirm safety and performance of the WaveCrest device in current medical practice in patients with non-valvular atrial fibrillation following minor system enhancements
Study Design	A prospective, multicenter, non-randomized, post-market clinical follow-up study to confirm safety and performance of the Coherex WaveCrest® Left Atrial Appendage Occlusion System in current medical practice in patients with non-valvular atrial fibrillation
Patient Population	Patients with non-valvular atrial fibrillation who are at increased risk for stroke

Study Endpoints	Safety and performance of the WaveCrest device through 45days.
	• Composite rate of:
	  o All-cause mortality
	  o Pericardial effusion requiring intervention
	  o Device embolization from the LAA
	  o Device thrombus
	  o Ischemic stroke
	• Device Success
	• Technical Success at implant
	• Procedural Success

Inclusion Criteria	The criteria for implant are in accordance to the current version of the Instructions for Use: 1. Non-valvular paroxysmal, persistent, or permanent atrial fibrillation 2. 18 years of age or older 3. LAA anatomy amenable to treatment by percutaneous techniques 4. Risk factors for potential thrombus formation in the LAA 5. Willing to participate in the required follow-up visits and tests 6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the EC at the study site
Exclusion Criteria	1. Known contraindication to percutaneous transseptal intervention 2. Left atrial appendage anatomy or size that will not allow appropriate implantation of the WaveCrest Implant 3. Intracardiac thrombus or other cardiac abnormality visualized prior to implant that would significantly impact procedural safety 4. Mitral valve stenosis < 1.5 cm^2 or any stenosis consistent with rheumatic valvular disease or history of mitral valve replacement or

	repair 5. Known contraindication and/or allergy to nickel 6. Known active bacterial infection (i.e., sepsis, endocarditis) 7. Any known medical condition or overall health of the subject that could adversely affect procedural safety or potentially prevent the patient from completing all study required visits and tests. 8. Pregnant or breastfeeding women due to the risk of exposure to x-rays and medications associated with the implant procedure.
Number of Study Sites	Up to 15 study sites will participate in the study in Europe
Sample Size	The sample size will include up to 65 enrolled subjects.
Enrollment Phase	The enrollment phase is expected to last between 18 and 20 months
Follow-up Evaluations	Office visit at 45 days. A transesophageal echocardiogram (TEE) will be performed at the 45-day visit.
Clinical Visits/Testing	**At baseline**: • History and physical exam (This is referring to the physical examination or 'check-up' of the patient for signs of disease or symptoms) • Blood work (including serum pregnancy test and INR if applicable) • Baseline transesophageal echocardiogram (TEE) (may be performed immediately prior to the procedure) • Questionnaire for Verifying Stroke-Free Status (QVSFS) • Patients with a history of stroke or TIA or a baseline QVSFS score > 0: o Assessment by a neurologist or person qualified to perform neurological assessments is recommended, per physician's judgment o Trained study personnel should administer the Modified Rankin Scale (Appendix IV) o Brain imaging (CT or MRI): results may be collected if brain imaging is done prior to implant as part of routine practice or if imaging was done at the time of the prior stroke. • CHA_2DS_2-VASc score **At Procedure**: • Follow Instructions For Use (IFU) for device implantation o TEE o Angiogram o Adverse event assessment **At discharge**: • Medication assessment

	• Adverse event evaluation • QVSFS Questionnaire **45 Day Follow-up (± 15 days)** • Physical exam (This is referring to the physical examination or 'check-up' of the patient for signs of disease or symptoms) • TEE • Medication assessment • Adverse event evaluation • QVSFS questionnaire

Neurological Assessment	If there is any concern for stroke (at scheduled visits, QVSFS results in a score > 0), a visit with neurologist or physician certified to assess neurological status is recommended, per physician's judgment.
	• If stroke is suspected and/or confirmed
	  o Trained study personnel should administer the Modified Rankin Scale (Appendix IV)
	  o Brain imaging (MRI, unless contraindicated, then CT): results may be collected if brain imaging is done as part of routine practice.
	• If stroke is confirmed, results of appropriate investigations done as part of routine practice, including transesophageal echocardiogram, to determine stroke etiology will be collected.

Medication regimen and Post-Procedure Care	• Patients on anticoagulants prior to implant may continue their pre-procedure regimens of anticoagulation at the discretion of the implanting physician • Patients should be advised to use appropriate endocarditis antibiotic prophylaxis for future dental and surgical procedures for at least 6 months post-implant • Patients who are not on anticoagulants should receive clopidogrel 75 mg per day for 90 days post implant • All patients should be maintained on 75 mg - 325 mg of aspirin per day indefinitely except those on anticoagulation. A lower dose aspirin is recommended while patients are on clopidogrel. • Patients should have follow-up visit at 45 days and standard of care imaging, including TEE to assess device position and LAA closure. • Patients should be followed in accordance with recommendations for treatment of atrial fibrillation

Contacts:

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2.0 Introduction

This document is a Clinical Investigational Plan (CIP) for the WAVECREST PMCF Study. The WAVECREST PMCF Study is a prospective, non-randomized, multicenter study to evaluate safety and performance of the Coherex WaveCrest Left Atrial Appendage (LAA) Occlusion System in the current medical practice setting in patients with non-valvular atrial fibrillation. Up to 65 subjects may be enrolled at up to 15 study sites in Europe. Patients will be followed through 45 days post-procedure.
The Sponsor shall maintain an updated list of participating investigators and study sites approved for participation by the relevant Ethics Committees (EC), which will be kept separately from the Clinical Investigational Plan.

3.0 Background

Normal heart contractions begin as electrical impulses in an area of the right atrium called the sinoatrial node. As an impulse travels through the atria, it produces a coordinated atrial muscular contraction that pumps blood through the atrioventricular (AV) valves into the ventricles. The electrical impulse passes to the AV node in the muscle wall between the two ventricles, producing a coordinated ventricular muscular contraction that pumps blood to the lungs and the systemic circulation. This orderly process is repeated billions of times in a normal lifetime.[1]

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[2] AF is usually associated with underlying heart disease (of almost any cause) that may result in multiple electrical atrial impulses. These impulses arise from and travel through the atria at different times, producing disorganized, chaotic, and rapid atrial contractions that lead to conduction of irregular impulses to the ventricles.[3] The atria become ineffective, dilated, and the normal flow of blood through them is significantly altered.[4]

Atrial fibrillation is classified as valvular, non-valvular, or lone. Non-valvular AF refers to cases without rheumatic mitral valve disease, prosthetic heart valve, or valve repair. Non-valvular AF can be further classified according to the AHA/ACC/ESC guidelines as paroxysmal, persistent, and/or permanent. Paroxysmal AF has been reported in an estimated 25 to 90% of subjects with AF[5,6,7,8,9] although 90% of cases of paroxysmal AF are asymptomatic and therefore the prevalence may not be known[10]. Paroxysmal AF terminates spontaneously whereas persistent AF is sustained for a minimum of seven days. Persistent or paroxysmal AF, if sustained for greater than a year, may lead to permanent AF.The left atrial appendage (LAA) is believed to function as a decompression chamber during left ventricular systole and other periods when left atrial pressure is elevated. The alteration in blood flow in AF patients has adverse consequences related to a reduction in cardiac output and to atrial and LAA thrombus formation that can lead to systemic embolization including stroke.[1,11,12] Thrombus may form within the LAA perhaps because of its shape and trabeculations, which predispose to blood stasis. Echocardiography and autopsy studies have shown that the LAA is the source of thrombi in more than 90% of non-valvular AF patients who experience stroke.[13,14,15]

Atrial fibrillation is responsible for 15% to 20% of ischemic stroke (Crystal 2004). AF accounts for one-fourth of all strokes in the elderly . The risk of stroke in subjects with non-valvular AF is

approximately 5% per year in subjects over 76 years of age (AF investigators Arch Intern Med 1994). Based on risk factors and treatment or the lack thereof, the risk of stroke can be as high as 18.2% per year in select subjects (Gage 2001).

3.1 Oral Anticoagulant Therapy

Guidelines recommend chronic anticoagulation for patients with non-valvular AF at risk of stroke.[16,17,18] Anticoagulation therapy with the Vitamin K antagonist, warfarin, has been shown to lower the risk of clinical thromboembolism in virtually all patients with AF, including all levels of risk, and irrespective of type (paroxysmal, persistent, or chronic).[19,20,21,22,23] Despite its proven efficacy, warfarin is often not well tolerated by patients, and has a very narrow therapeutic range and high risk of bleeding complications. Patients on long-term warfarin also experience numerous drug-drug, drug-supplement, and drug-food interactions and need frequent international normalized ratio (INR) assessments. Only about 50% of patients who are eligible for long-term warfarin are treated with it.

[a,24,25] One review of antithrombotic therapy in high-risk AF patients before admission for stroke (Registry of the Canadian Stroke Network) revealed that 29% of patients were not receiving any antithrombotic therapy, and only about one quarter of the 39% receiving warfarin (i.e., 10% of acute stroke patients with known AF) achieved therapeutic INR levels.[26] In a recent large national assessment of warfarin therapy use involving 138,319 patients in the US and 2,683,674 INR results, the reported mean time in therapeutic range was only 53.7%.[27] Additionally, approximately 20% of patients with AF in whom warfarin is recommended have a contraindication to warfarin (e.g., systemic or intracranial bleeding, potential for non-compliance with therapy, pregnancy, hypersensitivity).[28,29,30]

Randomized trials of novel anticoagulants (NOACs) such as direct thrombin inhibitor (dabigatran), and direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) against warfarin have demonstrated a reduction in thrombotic and hemorrhagic stroke when compared with warfarin.[31,32,33,34] NOACs have a more predictable pharmacokinetic profile than warfarin, fewer drug-drug and drug-food interactions, and do not require INR assessments. NOACs have also generally demonstrated a significant reduction in major bleeding when compared with warfarin, including an important reduction in intracranial hemorrhage. Several NOACs have received market approval for stroke risk reduction in non-valvular AF patients. However, bleeding related to the use of NOACs remains a clinically significant issue.[35,36,37] This bleeding risk increases with age, decreased creatinine clearance and concomitant aspirin use.[35] The randomized NOAC trials also reported significant discontinuation rates for both NOACs and warfarin (>20% at 2 years). The fundamental challenge in AF patients is long-term stroke prevention with no significant increased risk of major bleeding.

[a] Approved FDA Medication Guide found at:
http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088578.pdf

3.2 Risk-Stratification

Decision-making regarding the initiation of anticoagulant medication requires tools to predict both embolic and bleeding risk. Risk stratification for embolization in patients with non-valvular AF can be performed using both clinical and echocardiographic parameters. These parameters have been derived from both randomized trials and community cohorts. To identify AF patients at risk for stroke, the Atrial Fibrillation Investigators (AFI) pooled and analyzed data from five randomized stroke prevention trials[13,19,20,21,22] in patients with non-valvular AF.[38] The resulting $CHADS_2$ scoring system[39,40] has until recently been recommended for use to estimate embolic stroke risk in AF patients. **$CHADS_2$** is an acronym created from the first letter of five clinical parameters: **C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes mellitus, and prior **S**troke/TIA/Thromboembolism. The $CHADS_2$ score ranges from 0 to 6. A limitation of the $CHADS_2$ score is that a subset of patients with a $CHADS_2$ score of 1 may have other risk factors for embolic stroke that are not accounted for. This limitation is overcome by the use of the **CHA_2DS_2-VASc** score (which gives an additional point each for **V**ascular disease, **A**ge 65 to 74 years, and female **S**ex).[41] The CHA_2DS_2-VASc score ranges from 0 to 9. The CHA_2DS_2-VASc scoring system can be used to reliably identify truly low risk patients, who can be managed without antithrombotic therapy (i.e., patients with CHA_2DS_2-VASc score of 0).[40] **Table 1** explains the $CHADS_2$ and CHA_2DS_2-VASc scoring systems.

Table 1: $CHADS_2$ and CHA_2DS_2-VASc Scoring Systems

$CHADS_2$		**CHA_2DS_2-VASc**	
Risk Factor	**Points**	**Risk Factor**	**Points**
Congestive Heart Failure	1	Congestive Heart Failure[a]	1
Hypertension	1	Hypertension	1
Age ≥ 75 years	1	Age ≥ 75 years	2
Diabetes Mellitus	1	Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2	Stroke/TIA/Thromboembolism	2
		Vascular Disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
		Age 65 to 74 years	1
		Female	1
Maximum Score	6	Maximum Score	9

[a] Heart failure with reduced ejection fraction or recent heart failure hospitalization (irrespective of ejection fraction)

Table 2 shows stroke risks for the CHA_2DS_2-VASc scoring system.[16]

Table 2: Adjusted Stroke Rate by CHA_2DS_2-VASc Score

CHA_2DS_2-VAsc Score	Adjusted Stroke Rate (% per year)
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

3.3 LAA Occlusion or Exclusion

There have been a number of developments in occlusion or exclusion of the LAA via surgical or percutaneous means.

3.3.1 Surgical Approaches

Surgical ligation or amputation of the LAA has been performed almost since the inception of open heart surgery in the 1950s but it is only performed in patients who are undergoing cardiac surgery for other reasons (e.g., valve repair or replacement). The AHA-ACC valvular heart disease guidelines state that ligation or amputation is commonly performed in patients with AF undergoing mitral valve surgery with the aim or reducing the risk of thromboembolic events.[42] Limited data suggest that the surgical approach to LAA ligation or amputation can reduce the risk of stroke. In a non-randomized observational study of 205 patients who underwent mitral valve replacement, ligation of the LAA was performed in 58 patients.[43] After an average of almost six years, the incidence of an embolic event in patients with LAA ligation was significantly lower than in patients who underwent only mitral valve replacement (3% versus 17%, odds ratio 0.15, which fell to 0.08 if the patients with incomplete ligation were included in the group without ligation). However, surgical LAA suture-based ligation may be incomplete in many cases, resulting in continued risk for thromboembolism from the LAA.[44,45,46] Surgical clips and staplers are preferred approaches to surgical LAA closure. One minimally invasive surgical approach is the AtriClip LAA Exclusion System (AtriCure, West Chester, OH, USA) implant. This device has been approved in Europe (2009) and the United States (2010). The device is indicated for the exclusion of the LAA in conjunction with other open cardiac surgical procedures. In addition to open surgical approaches, thoracoscopic occlusion of the LAA using an endoloop snare has been described in 15 patients with chronic or intermittent AF.[47] The procedure was successful in 14. However, two strokes occurred in up to 60 months of follow-up (i.e., stroke rate 4% per year): 1 fatal stroke occurred 55 months after surgery and 1 disabling stroke 3 months after surgery.

3.3.2 Impetus for Percutaneous Approaches

Although the efficacy of oral anticoagulant (OAC) therapy in stroke risk reduction has been proven, OACs are often not well tolerated by patients. Indeed, many risk factors (e.g., age, prior stroke, hypertension) for stroke are also risk factors for bleeding on OAC. Non-pharmacologic management in the form of surgical ligation or amputation and thoracoscopic occlusion are inconsistently effective and often require chronic anticoagulation. Additionally, open surgical approaches to LAA ligation or amputation are only undertaken in patients who are undergoing open cardiac surgery for other reasons. Minimally invasive catheter-based therapies are a desirable alternative for patients who do not have indications for open heart surgery and are intolerant of or contraindicated for OAC. The recent EHRA/EAPCI expert consensus statement recognizes the role of catheter-based LAA occlusion, especially in patients who refuse OACs.[18]

3.3.3 Percutaneous LAA Occlusion Devices

The Coherex WaveCrest® device is a catheter-based device for the percutaneous occlusion of the LAA. The Watchman (Boston Scientific, Marlborough, MA, USA) and Amplatzer Cardiac Plug and Amulet (St. Jude Medical, St. Paul, MN, USA) are other percutaneous LAA occlusion devices. These devices are CE marked and available for commercial use in Europe. Another percutaneous device is the LARIAT device (SentreHEART, Redwood City, CA, USA), which uses a combined pericardial and endocardial procedure to ligate the LAA. This device has been approved in the United States through a 510(k) for soft-tissue approximation and/or ligation with a pre-tied polyester suture. Because this device originally received regulatory approval as a ligation device, it is marketed as such; however, it is routinely and exclusively used throughout the world for LAA closure as a means of reducing AF mediated stroke.

3.4 Clinical Experience with the WaveCrest Device

The WaveCrest device was studied in the Coherex WAVECREST 1 Left Atrial Appendage (LAA) Occlusion Study (WAVECREST 1 Study). One-hundred fifty-five (155) patients were treated with the WaveCrest LAA occlusion device at 19 investigational sites in Europe, Australia and New Zealand. Three device versions were studied: **Version 1.1** (N=9), **Version 1.2** (N=73) (enhancements were made to the device and user training), **Version 1.3** (N=73) (enhancements were made to the anchor frame and delivery catheter). The study enrolled elderly patients with an average $CHADS_2$ Score of 2.5 and at high risk of stroke. More than half (65%) the patients were contraindicated for anticoagulation. Clinical results on device **Version 1.3**, which is the device which received CE mark are as follows: procedural success was achieved in a majority of patients (96%). Procedure duration averaged 68 minutes, with forty-seven percent (47%) of procedures requiring no device repositioning. On average, 1.3 devices were used (i.e., attempted) per patient. Pericardial effusions/tamponade occurred at a rate of 2.7% with none requiring surgical intervention. No safety-related events occurred after 45 days. At 45 days, LAA closure, defined in the study as residual gap ≤3mm, occurred in 97% of patients. With LAA closure defined as residual gap ≤5mm, LAA closure rate at 45 days was 100%. There were no unanticipated adverse events or unanticipated adverse device effects.

The WaveCrest device received the CE Mark in August 2013 and became available commercially in Europe in October 2013. Procedural success was high during limited market release, with 88/92 (96%) procedural success rate through July 2014. Pericardial effusions occurred at a rate of 3.3% (3/92). There was one device embolization (1.1%). In 2 patients (2.2%), a thrombus was discovered on a follow-up TEE. There were no procedural strokes. In 2 patients, there was damage to the inner liner of the Delivery Sheath. Both cases were considered "incidents" and warranted a Field Safety Notice (FSN) and Field Safety Corrective Action (FSCA) in August 2014, resulting in modification to the Delivery Sheath liner. In addition, some minor enhancements were made to the device. These device enhancements were approved in a Change Notification to the original CE mark.

3.5 Rationale to Conduct Clinical Study

The WAVECREST PMCF Study is intended to evaluate the safety and performance of Coherex's WaveCrest LAA Occlusion System in current medical practice through 45 day follow-up following minor system enhancements. Forty-five days is the recommended follow-up period in the IFU and the recommended standard of care in clinical practice for this type of procedure. This timeframe provides an appropriate length of time from the implant procedure to capture any procedural safety-related events based on the canine study and prior clinical studies. Performance of the device is demonstrated by procedural and device success at implant.

The WaveCrest device is passive in nature once it is deployed in the LAA. Initially the anchors hold the device in position, however, tissue in-growth (endothelialization) begins immediately in the occluder material once the device is implanted. Canine testing showed the safety and performance of the device modifications during the implant procedure and complete implant endothelialization by 30 days**.** The WAVECREST 1 study and the initial limited market release have effectively demonstrated the safety and performance profile during implant and long-term safety of the occluder materials in clinical use .

4.0 Identification of the Device

4.1 Manufacturer details

The Coherex WaveCrest Left Atrial Appendage Occlusion System ("WaveCrest device") is a CE marked device manufactured by

Coherex Medical, Inc.
3598 West 1820 South
Salt Lake City, UT 84104
United States of America

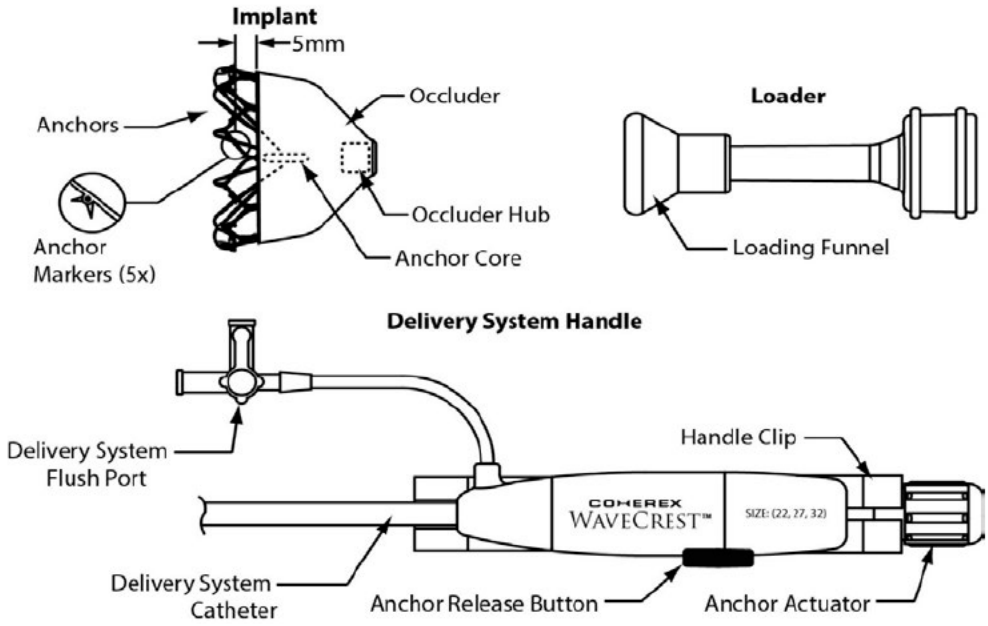
The WaveCrest device is developed in accordance with EN: ISO13485 standard.

4.2 Device Description

The WaveCrest device is designed to occlude the left atrial appendage (LAA) and consists of the following components: the device, which is pre-loaded on the delivery system, and the Delivery Sheath which is packaged separately. The device, consisting of a separate occluder and anchors, is the implantable component of the system. The device is constructed from a laser-cut nitinol framework. Parts of this framework are constructed with titanium components and also contain tantalum radiopaque markers. The occlusive membrane is composite construction. The surface of the membrane that is exposed to the left atrium is covered with ePTFE and is designed to resist thrombus buildup. The surface of the membrane that is exposed to the LAA consists of polyurethane foam, which is designed to promote rapid tissue growth.

Figure 1: Coherex Left Atrial Appendage Implant

Figure 2: Coherex Left Atrial Appendage Implant and Handle



The delivery system for the implant consists of a delivery catheter and a proximal control handle. The delivery catheter is constructed from polyurethane extrusions, stainless steel components, and polyester and PTFE materials that are common to medical catheter construction. The proximal control handle is designed to actuate the anchors through the catheter and to detach the implant from the system. The Coherex WaveCrest® Left Atrial Appendage Occlusion System Delivery Sheath is designed to facilitate the delivery of the implant. The Delivery Sheath includes a dilator used for insertion. The Delivery Sheath is designed to be used exclusively with the Coherex WaveCrest Left Atrial Appendage Occlusion System.

The implant is delivered percutaneously via the femoral vein through a transseptal puncture into the LAA. A separate transseptal puncture system is required. The occluder is designed to be unsheathed inside the ostium of the LAA. When unsheathed, only the occlusive portion of the device is exposed. The structure of this portion is very soft to reduce the risk of perforation or effusion. The occluder may be positioned within the LAA to achieve optimal occlusion. After positioning, the occluder is anchored in place by extending the anchors from the central hub of the device. A distal injection port allows contrast to travel through the delivery system to the distal side of the occluder to allow visualization of the position, stability and effectiveness of occlusion prior to release with fluoroscopy. Anchoring and occlusion can also be assessed by TEE. When anchoring and occlusion are confirmed, the implant is detached and left within the LAA and the Delivery Sheath along with the Delivery Catheter are removed. The WaveCrest device implant is available in diameter sizes of 22, 27 and 32 mm.
More detailed information on the device can be found in the latest version of the approved Instructions for Use and the updated version of the Investigator's Brochure.

4.3 Intended Indication

The Coherex WaveCrest Left Atrial Appendage Occlusion System is approved for use for the closure of the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation, who are at increased risk for stroke.

4.4 Device Traceability

To ensure traceability of the WaveCrest devices used within the study, the following information will be documented:

- Model and Lot number
- Date of implant

Process for order, receipt and return of the CE-marked devices is in accordance with the commercial process. A Patient Implant Card will be handed to each patient successfully implanted with the device.

5.0 Study Design

5.1 Purpose

This study is designed to confirm the safety and performance of the Coherex WaveCrest LAA Occlusion System in current medical practice through 45 day follow-up following minor system enhancements.

5.1.1 Number of subjects

Up to 65 subjects will be enrolled in the study at up to 15 study sites in Europe.

5.1.2 Estimated study duration

Enrollment in the study will be concluded in approximately 18 - 20 months after the first subject is enrolled. Total duration including follow-up visits is expected to be 22 months.

5.2 Endpoints

Safety and performance of the WaveCrest device through 45 days follow-up will include the following endpoints:

- Composite rate of:
  - All-cause mortality
  - Pericardial effusion requiring intervention
  - Device embolization (major)
  - Device thrombus
  - Ischemic stroke

- Device Success - Device deployed and implanted in the correct position

- Technical Success at implant
  - Occlusion of the LAA
  - No device-related complications
  - No leak >5mm on color Doppler TEE

- Procedural Success
  - Technical success
  - No procedure-related complications except uncomplicated (minor) device embolization (resolved by percutaneous retrieval during the procedure without surgical intervention or damage to surrounding cardiovascular structures)

5.3 Inclusion and Exclusion Criteria

The criteria for implant are in conformity with the current version of the Instructions for Use of the CE-marked device:

5.3.1 Inclusion Criteria

1. Non-valvular paroxysmal, persistent, or permanent atrial fibrillation
2. 18 years of age or older
3. LAA anatomy amenable to treatment by percutaneous techniques
4. Risk factors for potential thrombus formation in the LAA
5. Willing to participate in the required follow-up visits and tests
6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the EC at the study site.

5.3.2 Exclusion Criteria

1. Known contraindication to percutaneous transseptal intervention
2. Left atrial appendage anatomy or size that will not allow appropriate implantation of the WaveCrest Implant
3. Intracardiac thrombus or other cardiac abnormality visualized prior to implant that would significantly impact procedural safety
4. Mitral valve stenosis < 1.5 cm^2 or any stenosis consistent with rheumatic valvular disease or history of mitral valve replacement or repair
5. Known contraindication and/or allergy to nickel
6. Known active bacterial infection (i.e., sepsis, endocarditis)
7. Any known medical condition or overall health of the subject that could adversely affect procedural safety or potentially prevent the patient from completing all study required visits and tests.
8. Pregnant or breastfeeding women due to the risk of exposure to x-rays and medications associated with the implant procedure.

5.4 Subject Population

Patients with non-valvular atrial fibrillation who are at increased risk for stroke.

No subjects belonging to a vulnerable population (see definition of vulnerable population in **Appendix I:** Acronyms and Definitions) will participate in the clinical study.

6.0 Study Procedures

The clinical study shall be conducted in accordance with the CIP reflecting current medical practices and approved IFU. All parties participating in the conduct of the clinical study shall be qualified by education, training, or experience to perform their tasks and this shall be documented appropriately.

The clinical study shall not commence until Coherex Medical receives written approval from the relevant EC of each study site as necessary.

6.1 Site and Investigator Selection

Sites will be selected for this study based on the qualification and experience of the implanting investigator. The implanting investigator must have had experience in transseptal puncture

procedures and percutaneous LAA closure techniques. Intended users must have completed the WaveCrest Physician Training program. Investigators must provide a financial disclosure statement and sign an Investigator Agreement and/or a site agreement as applicable. Site selection will also depend on the availability of experienced staff to conduct clinical research. Study personnel will be responsible for administering the Questionnaire for Verifying Stroke-Free Status (QVSFS). The study site will have a neurologist or other study personnel who are trained to administer the Modified Rankin Scale.

6.2 Training of Investigators and Study Personnel

Sponsor will provide training on the Clinical Investigational Plan and Case Report Form (CRF) completion.

Additionally, Sponsor will provide training to echocardiographers assigned to the study. Sponsor training on the WaveCrest implant procedure will include:

- an on-line self-study simulation module which will present device and procedure steps,
- training presentation focusing on anatomical considerations, device details and required procedural steps, and
- table-top training with model to simulate implant procedure steps.

A record of training activities and the completed training process will be kept in a training log provided by the Sponsor.

6.3 Informed Consent

All subjects must sign and date the EC approved informed consent prior to undergoing any study-specific tests, assessments or procedures. Investigator or designated study personnel will explain the nature and scope of the study, potential risks and benefits of participation, and answer any questions from the subject. Study personnel must explain that agreeing to participate in the study and signing an informed consent form does not guarantee study participation. The subject must be provided ample time to read and understand the informed consent form and to consider participation in the clinical study. If the subject agrees to participate, the informed consent form must be signed and dated by the subject. The authorized person obtaining informed consent must sign, and date the informed consent prior to conducting any study-specific tests, assessments or procedures. The consent process, provision of a copy to the subject, and date and time of consent must be documented in the subject's medical records. Subject information may be entered in the CRF only after the subject has provided informed consent.

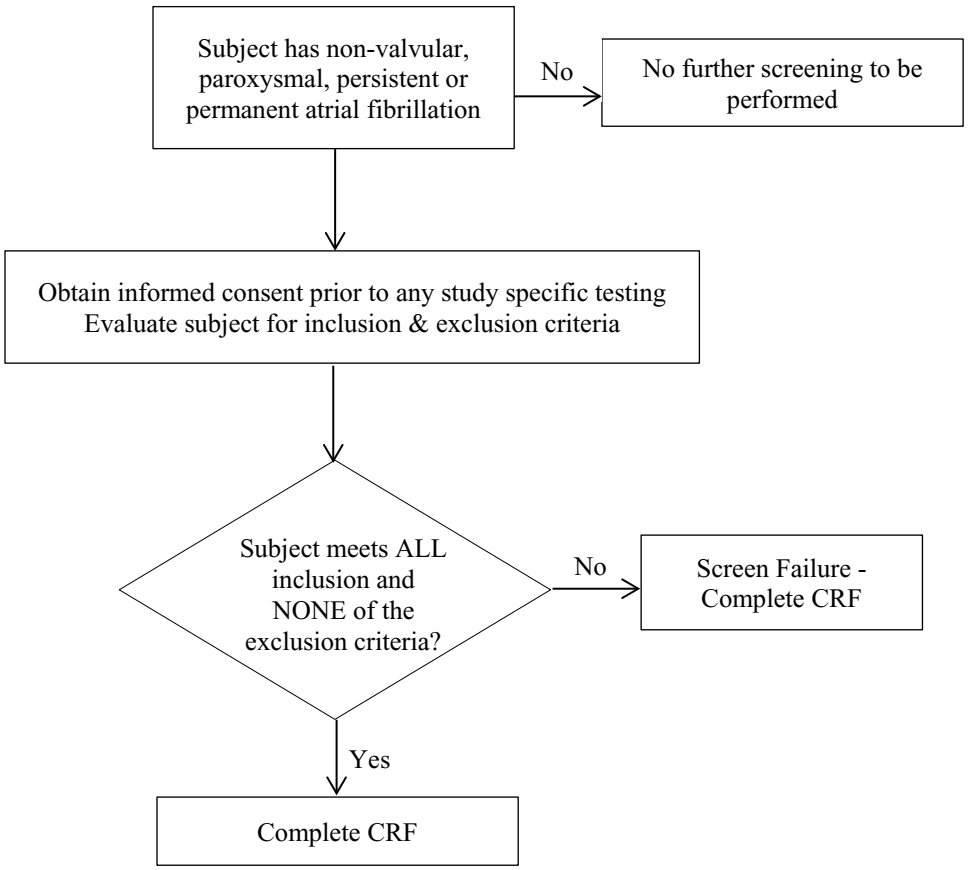
Subject confidentiality will be maintained throughout the clinical study in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the study may be made available to authorized third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

A Delegation of Authority Log and a Sponsor-Representative Log will be maintained and updated throughout the study to indicate who the authorized persons are for each task within the study and for whom access to patient confidential data is authorized.

6.4 Subject Selection and Screening

Sites may begin screening subjects for the study upon receiving EC approval. Screening for the study must be performed per Inclusion and Exclusion Criteria based on medical records at the study site (**Figure 3** below).

Figure 3: Patient Screening



6.5 Baseline Procedures

- Document medical history
- Perform physical exam (This is referring to the physical examination or 'check-up' of the patient for signs of disease or symptoms)
- Blood work (including INR and serum pregnancy (as necessary))
- CHA_2DS_2-VASc score (see **Appendix II** for calculation of CHA_2DS_2-VASc score)

- A study staff member who is trained must administer QVSFS (**Appendix III:** Questionnaire for Verifying Stroke-Free Status**)**
- In the event of history of stroke or TIA or QVSFS score > 0 a trained study staff member must administer the Modified Rankin Scale. (**Appendix IV:** Neurologic Assessments). A visit to the neurologist or physician qualified to perform neurologic assessment is recommended, per physician's judgment.
- In the event of history of stroke, brain imaging (CT or MRI) results may be collected if brain imaging is done prior to implant as part of routine practice or if imaging was done at the time of the prior stroke (at any time).
- Perform baseline TEE (may be performed immediately prior to the procedure)

6.6 Point of enrollment

Subjects are considered enrolled in the study when the subject has properly signed the approved Informed Consent. If the patient doesn't meet all of the inclusion criteria or meets one of the exclusion criteria, the subject is considered a screen failure. The appropriate forms in EDC need to be completed.
Subjects are considered enrolled in the study and Intent-to-Treat is established when the subject has properly signed the approved Informed Consent, has met all of the inclusion criteria and none of the exclusion criteria, and the Coherex Delivery sheath has been inserted into the subject's femoral vein.
If the device is not implanted for any reason, the patient will be considered a Failure to Implant and discontinued from the study.
All adverse events as of enrollment and prior to patient discontinuation will be collected.

Absence of intracardiac thrombus must be confirmed on the TEE performed during the implant procedure. If thrombus is observed, the implant procedure must be postponed. The subject may be rescreened after the thrombus has resolved.

6.7 Recommended Pre-Procedure Medications

Recommended pre-procedure medications are in accordance with the applicable IFU recommendations:

- **Anticoagulation Therapy**
  Subjects on anticoagulants prior to implant may continue their pre-procedure regimens of anticoagulation at the discretion of the implanting physician. Subjects currently taking anticoagulation for history of stroke or TIA may suspend anticoagulation 3 days prior to the implant procedure, at the investigator's discretion. If the patient has been on anticoagulation within 7 days of the procedure it is recommended that the patient's INR is checked within 24 hours prior to implant and that the implant procedure should not be performed if the subject's INR $\geq$ 2.0.
- **Aspirin Therapy**
  Administration of aspirin one day prior to the procedure is recommended at the physician's discretion.

- **Antibiotic Therapy**
  Use of antibiotic for endocarditis prophylaxis prior to the implant procedure is recommended per the site's standard of care.

6.8 Implant Procedure

Follow the Coherex WaveCrest LAA Occlusion System Instructions for Use (IFU) for the implant procedure.

- Perform Implant Procedure
  - Perform a transseptal puncture using standard catheterization methods.
  - A TEE should be performed prior to the procedure to determine if the anatomy is appropriate for implantation and to confirm the absence of thrombus in the LAA
  - Images of the LAA ostium should be taken to confirm minimum and maximum width measurements prior to selecting a device size.
  - The subject should be heparinized to maintain an activated clotting time (ACT) >250 seconds for the duration of the procedure (prior to introduction of the implant and until sheath is withdrawn). Bivalirudin may be used if heparin is contraindicated. ACT measurement is not required if bivalirudin is used. *Note: Bivalirudin should not be used if the INR is >2.0.*
  - Confirm and record the position and stability of the implant using both fluoroscopy and TEE before and after device release.
- Administer recommended post-implant medications per physician's discretion as subject's condition dictates.
- Provide subject with Patient Implant Card (this card will provide the investigator's contact information and device identification number)
- Record antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations as appropriate

6.9 Discharge

Before the subject is discharged from hospital:

- Administer QVSFS questionnaire
  - If there is any concern for stroke, a visit to the neurologist or physician qualified to perform neurologic assessment is recommended
- Record antiplatelet and anticoagulant medications.
- Record adverse events, device malfunctions and protocol deviations as appropriate.
- Discharge subject on 75-325mg aspirin daily and 75mg clopidogrel.

Table 4 summarizes the post-procedure anticoagulation and antiplatelet regimen.

Note: Subjects who are not implanted with a device should be followed through hospital discharge for adverse events and appropriate CRF to be completed.

6.10 45-Day Office Visit (± 15 days)

At the 45-day office visit:

- Perform physical exam (This is referring to the physical examination or 'check-up' of the patient for signs of disease or symptoms).
- Study personnel must administer the QVSFS;
  - If QVSFS score > 0, a visit to the neurologist or physician qualified to perform neurologic assessment as soon as possible following QVSFS administration is recommended. The modified Rankin stroke scales should be administered by trained study personnel.
- Perform a TEE following the Echocardiography Protocol.
- If patient has been on anticoagulation, cessation of anticoagulation is at physician discretion provided flow around the implant, with correlate 2D residual gap, is demonstrated on TEE to be ≤ 5mm. At the time the subject stops anticoagulation clopidogrel 75mg daily should be started and should continue until 90 days post-implant (prasugrel or ticagrelor may be used in place of clopidogrel, but must not be used with anticoagulation).
- Instruct subject to remain on 75 -325 mg aspirin indefinitely. **Table 4** summarizes the post-procedure anticoagulation and antiplatelet regimen.
- Record antiplatelet and anticoagulant medications.
- Record protocol defined adverse events, device malfunctions and protocol deviations as appropriate.

The schedule of assessments is listed below in **Table 3**.

Table 3: Schedule of Assessments

Assessment	Screening/ Baseline	Treatment Visit (Through discharge)	45 Day Visit ± 15 days
Medical history	X		
Physical exam*	X		X
Pre-Procedure blood work	X		
CHA_2DS_2-VASc score	X		
TEE	X	X	X
QVSFS	X	X	X
Antiplatelet and Anticoagulant Medication Review	X	X	X
Adverse Event Monitoring[a]	X	X	X
In case QVSFS > 0 or history of stroke or suspected stroke/TIA			
Neurologic exam[b]	X		X
Modified Rankin Scale	X		X
Brain Imaging (MRI – if contraindicated, then CT)	X[c]		X[d]

[a] Adverse event monitoring is initiated upon vascular access with Delivery Sheath.

[b] Neurologic visit/exam at baseline for history of stroke or TIA or anytime QVSFS > 0 is recommended, per physician's judgment

[c] Brain imaging results may be collected if imaging is performed as part of routine practice or performed at time of prior stroke (at any time)
[d] Brain imaging results may be collected if imaging is performed as part of routine practice
[*] This is referring to the physical examination or 'check-up' of the patient for signs of disease or symptoms

6.11 Unscheduled Neurologic Visit

A neurologic visit may be triggered by subject symptoms, if there is any concern for stroke (at scheduled visits, QVSFS results in a score > 0 or if a neurologist or a physician certified to assess neurological status suspects a stroke). It is recommended that a neurologist or physician certified to assess neurological status examines the subject, per physician's judgment.

- If stroke is suspected or confirmed:
  - Modified Rankin Scale (see **Appendix IV:** Neurologic Assessments*)* must be administered by trained study personnel
  - Brain imaging study (MRI, CT) results may be collected if imaging is performed as part of routine practice or performed at time of prior stroke (at any time).
- If stroke is confirmed**:**
  - Results of appropriate investigations done as part of routine practice, including TEE, to determine stroke etiology, will be collected (see **Appendix I:** Acronyms and Definitions for stroke definition and etiology).

Table 4: Recommended Adjunctive Antiplatelet and Anticoagulant Medication Regimen for Successful Device Implant (per IFU)[a]

Visit	Anticoagulation	Aspirin	Clopidogrel
Discharge to 45-days if patient has been on anticoagulation prior to implant for history of stroke	Yes[d]	Per institutional practice [b]	No
Discharge to 90-days	No	Yes 75-325mg	Clopidogrel[c] 75mg
>90 days	No	Indefinitely	No

[a]For subjects not implanted with an LAA occlusion device, antiplatelet and anticoagulant medications will be per physician discretion.
[b]If patient remains on anticoagulation, aspirin is not recommended
[c] Prasugrel 5-10 mg QD or ticagrelor 90 mg BID may be used in place of clopidogrel in subjects unable to take clopidogrel (but may not be used with anticoagulation).
[d] if patient remains on anticoagulation, cessation of anticoagulation remains at physician discretion if closure is demonstrated

6.12 Subject Discontinuation

Participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Possible reasons for discontinuation may include but may not be limited to the following:

- Voluntary withdrawal
- Participation is terminated by the investigator, although the subject consented, since participation is no longer medically appropriate
- Lost-to follow-up (defined below)

If a patient decides to withdraw from the study, effort must be made to continue monitoring for adverse events even if he/she declines to continue in the study. Discuss with the patient if he/she agrees with phone follow-up only for the purpose of recording adverse events or non-invasive review of records.

Subjects who discontinue participation prematurely will be included in the ITT analysis of results (safety and performance as appropriate) but will not be replaced.

Investigators must report subject withdrawals to their respective EC as defined by their institution's procedure.

6.13 Lost-to-Follow-up (LTFU)

If a subject misses scheduled follow-up visit, and study personnel make two unsuccessful documented attempts to contact the subject, the subject will be considered lost-to-follow-up.

6.14 End of Study Participation

Subjects will be considered to have ended participation in the study when they have completed 45 day follow-up or have discontinued from the study. The appropriate CRF must be completed for the subject when:

- the subject has completed 45 day follow-up, or
- the subject has died before follow-up is complete, or
- the subject has requested to withdraw from the trial with no further contact or review of charts.

6.15 Early Study / Site Termination

The Sponsor reserves the right to suspend or terminate the clinical study at any stage. Possible reasons for termination may include, but are not limited to:

- Slow/no inclusion of patients that could not be mitigated
- Unanticipated Adverse Device Effects (UADEs) present an unreasonable risk to subjects

If the study is terminated early, the Sponsor will provide a written statement to the investigators (to enable notification to the EC as applicable) and the ECs, as appropriate.

Should the study be terminated by the Sponsor, subjects must continue to be followed per routine hospital practice and device related adverse events must be reported per the manufacturer's procedures and applicable regulations.

The Sponsor may decide to suspend or prematurely terminate a study site (eg ,non-compliance or unmitigated lack of enrollment). If a study site is suspended or prematurely terminated, the Sponsor shall inform the investigator of the termination/suspension and the reason why. Also the reviewing EC will be informed, as required.

If an investigator voluntary decides to suspend or terminate participation, the relevant EC must be informed, as appropriate.

Should early termination occur, the investigator shall return all clinical study materials to the Sponsor and maintain study documentation and patient CRFs/data files for the period of time required by local regulations.

7.0 Protocol Compliance

7.1 Statement of Compliance

This study will be conducted in accordance with this CIP, the Declaration of Helsinki, good clinical practices and applicable regulations (ICH E6 GCP, ISO 14155:2011), and the appropriate regional and/or national regulations.

The protocol and informed consent must be approved by the appropriate EC of the respective study site, as appropriate.

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining EC approval.

In case additional requirements are imposed by the EC, those requirements will be followed, if appropriate. If any action is taken by an EC, and regulatory requirements with respect to the study, that information will be forwarded to Coherex Medical.

As Sponsor, Coherex Medical has taken up general device liability insurance in accordance with the requirements of the applicable legislation.

7.2 Protocol Deviations and non-compliance

A protocol deviation is defined as an instance of failure to intentionally or unintentionally follow the requirements of this Clinical Investigation Plan. The investigator and study personnel will not deviate from the protocol for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject, or to eliminate an apparent immediate hazard to the subject. In such an event, the investigator will notify Sponsor within 24 hours by phone or in writing.

In the event a protocol deviation has occurred, the appropriate CRF must be completed.
Investigators will inform their EC of protocol deviations in accordance with their specific EC reporting policies and procedures.

It is the investigator's responsibility to comply with this Clinical Investigation Plan, regulatory requirements and the Investigator Agreement. Evaluation of investigator compliance to this Clinical Investigation Plan, regulatory requirements and Investigator Agreement will be monitored by the Sponsor or designee. In the event an investigator is not compliant with this Clinical Investigation Plan, regulatory requirements or the Investigator Agreement, the investigator will be notified of the non-compliance. In the event of repeated non-compliance, the Sponsor will attempt to secure compliance by contacting the investigator (by telephone, email/letter, or visit). Repeated non-compliance despite these steps may result in further escalation in accordance with the Sponsor's procedures, including notification to the relevant EC and termination of the investigator's participation in the study.

8.0 Adverse Event, Adverse Device Effect, Device Deficiency

8.1 Adverse Event (AE)

An adverse event is 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 device. This definition includes events related to the procedures involved.

Note: Unchanged, chronic, non-worsening or pre-existing conditions are not adverse events.

The investigator must monitor and report the occurrence of adverse events for each subject. Adverse events, including the event description, date of onset, outcome, whether or not any medication changed or a hospitalization or intervention occurred, and whether the adverse event was resolved (if so, how, and date of resolution), must be reported on the appropriate CRF within 2 weeks. Every effort must be made to report the underlying condition or unifying diagnosis for the event. To avoid vague, ambiguous, or colloquial expressions, adverse events should be recorded in standard medical terminology rather than the subject's words. The appropriate CRF must be updated as additional information on the event is received.

All events must be followed until resolution or until a stable clinical endpoint is reached. The medical safety officer may decide if more follow up information is needed in case the event is not resolved at study completion.

Relatedness

For each event, the investigator will assess relationship to the device and the implant procedure. Relationship of an adverse event to the device and/or implant procedure will be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more-likely cause. Device and procedure relationship of each adverse event will be categorized according to five different levels of causality, adapted from MEDDEV guideline 2.7/3 rev 3 and as defined below:

- **Not related**: relationship to the device or procedure can be excluded when:
  - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has no temporal relationship with the use of the device or the procedures;
  - the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the event involves a body-site or an organ not expected to be affected by the device or procedure;
  - the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the device used for diagnosis, when applicable;
  - harms to the subject are not clearly due to use error;
  - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

- **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

- **Possible:** the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

- **Probable**: the relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

- **Causal relationship**: the event is associated with the device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with device use/application or procedures;
- the event involves a body-site or organ that
- the device or procedures are applied to;
- the device or procedures have an effect on;
- the event follows a known response pattern to the device (if the response pattern is previously known);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

In general, any event that occurs within 30 days is considered related to the procedure, unless clear signs are available that they are not.

The investigator will distinguish between adverse events related to the device and those related to the implant procedure. An adverse event can be related both to the implant procedure and the device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use/application.
In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The investigator will make the maximum effort to define and categorize the event and avoid these situations. Where the investigator remains uncertain about classifying the event, it should not exclude the relatedness and classify the event as "possible".

8.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an adverse event that:

a) Led to death,
b) Led to serious deterioration in health of the subject, that either resulted in:
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient hospitalization or prolongation of existing hospitalization, or
   4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

The following definitions will be used for defining in-patient or prolonged hospitalizations for SAE classification purposes:

- Prolonged hospitalization will be defined as prolongation of hospitalization due to change/worsening of patient's clinical status

- After initial procedure, subsequent hospitalization will be defined as ≥ 24 hours in duration or < 24 hours with medical intravenous therapy or surgical intervention
- A planned hospitalization or treatment for a pre-existing condition, or a procedure required by this Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event (e.g., non-emergent cardioversion). In case a planned procedure is performed after the patient is enrolled in the study without any complications the procedure should not be reported as an SAE, however, the procedure is to be reported as a non-serious event in EDC.

8.3 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

This definition includes any event resulting from the use error or from intentional misuse of the medical device.

8.4 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.5 Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the risk analysis plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects..

If the event is not serious, not life-threatening, not related to death or not related to device or procedure, it should not be considered unanticipated.

A UADE must be reported by the investigator to the **Sponsor immediately but no later than 24 hours** of the investigator's knowledge of the event, and to the EC per EC requirements.

8.6 Device Deficiency

A device deficiency is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Device deficiencies include malfunctions, use errors, and inadequate labeling.

8.7 Death

Subject deaths must be reported as soon as possible but no later than 24 hours on the appropriate CRF from the time study personnel become aware of the event. Deaths will be reported as cardiovascular or non-cardiovascular (**Appendix I:** Acronyms and Definitions). The investigator must report the death to the local EC according to the EC reporting requirements. In the event of subject death within 45 days of the implant procedure and an autopsy were performed, the autopsy report should be submitted to the Sponsor.

8.8 Reporting requirements

Adverse events are reported beginning from the time the patient is enrolled until patient participation has ended.
The investigator shall inform the Sponsor of all adverse events and device deficiencies as described in table below:

Event Classification	Recording Method	Timeline
Adverse Events, including ADE	Complete appropriate CRF form	As soon as possible or as per local regulations, but no later than 2 weeks of site awareness
Serious Adverse Events, including SADE	Complete appropriate CRF form Provide all necessary documentation needed	Immediately upon awareness of the event or became aware that the event met the definition of a SAE, but no later than 72 hours
Death	Complete appropriate CRF form	Within 24 hours
UADE	Complete appropriate CRF form	Immediately upon awareness of the event, but no later than 24 hours
Device deficiencies	Complete appropriate CRF form	Within 24 hours

The investigator is responsible for informing the EC of adverse events as required by local reporting requirements.

The Sponsor will submit on regular basis (unless otherwise indicated by the EC or recommended by the Sponsor's medical safety officer) to all participating investigators an update of reported events and device deficiencies occurred at the participating study site.

The Sponsor will ensure that all events and device deficiencies are reported to the relevant authorities per country specific regulations.

The Sponsor will continue safety surveillance and safety reporting until the last follow-up visit has been performed, the subject is deceased, the subject/investigator concludes his participation in the study or the subject/investigator withdraws the subject from the study.

The Sponsor is responsible for the classification of adverse events and shall review the investigator's assessment of all adverse events.
The Sponsor will determine and document in writing their seriousness and relationship to device.

8.9 Contact details

In case of questions for reporting of adverse events, the monitor responsible for the study site should be contacted site or the responsible Study Safety Lead for this study:

PPD

9.0 Monitoring

Sponsor or Sponsor's representatives will monitor the clinical study to ensure compliance with the Clinical Investigation Plan and applicable regulations, and accuracy of study data under Sponsor monitoring procedures. Source documentation must be available to substantiate proper informed consent procedures, adherence to the CIP, comprehensive reporting and follow-up of adverse events, accurate reporting of protocol deviations, and investigational device traceability. Monitoring will also verify that study data submitted on CRFs are complete and accurate. Data submitted on CRFs will be verified against source documents (medical records).

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance. On site monitoring will be conducted according to a pre-planned monitoring plan designed by the Sponsor.

The investigator will collaborate with the clinical monitor to schedule monitoring visits, provide a suitable environment for monitors to access study-related documents and source documents, and be available during monitoring visits. A monitoring visit sign-in log will be maintained at the study site.

10.0 Data Management

10.1 Data Handling and Record Keeping

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of her/his information shall be preserved in reports and when publishing any data.

Documents and data shall be produced and maintained in a way that assures control and traceability. As relevant, accuracy of translations shall be guaranteed and documented. All documents, and subsequent versions, related to the clinical study shall be version-dated and

identifiable, traceable and appropriately stored to provide a complete history of the clinical study.

Data collection will occur using an electronic database capture system (EDC) by study personnel trained on the CIP and CRF. Sponsor's expectation is for data to be entered by the study site in the CRF in a timely manner by authorized personnel as documented in a delegation of authority log.
The investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports. Data reported on CRFs shall be derived from source documents and be consistent with these source documents. Corrections to the CRFs will be performed by the investigator or designated study personnel. A record of study personnel authorized to perform CRF data entry or corrections will be maintained by the study site and provided to the Sponsor.

Sponsor or designee will regularly perform data review and database cleaning, including issuing queries.

Data are stored in a secure environment: the EDC application is 21 CFR part 11 compliant. Access to data is limited to authorized individuals.

Data protection will abide by regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. Data transfer outside the EU and to the US will be performed under adequate levels of protection and inspired by data transfer modalities at least as protective as the data protection laws within Europe.

10.2 Record Retention

The principal investigator (PI) will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the study site in accordance with local legislation and requirements.

The Investigator must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the study site, the investigator will notify the sponsor.

All data and documents will be made available upon request to the auditors mandated by the Sponsor to conduct audits and to relevant authorities inspectorates in case of an inspection.

The sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

11.0 Study Organization

A Physician Advisory Committee, consisting of physicians of varying specialties (interventional cardiology, electrophysiology, neurology) and a Sponsor representative, will be responsible for oversight of the scientific and operational aspects, and reporting of trial results. The committee will meet as needed to review trial progress and may advise the Sponsor on potential trial modifications during the trial conduct phase. The Physician Advisory Committee will also make recommendations regarding any publications arising from data generated from the trial.

The Sponsor's Medical Safety Officer (a physician by training) will review all adverse events reported within this clinical study and will provide recommendations to the Sponsor if needed.

12.0 Amendments to the Clinical Investigational Plan

This CIP, and any amendment, will follow Sponsor procedures for generation, approval and amendment of quality system documents. Amendments to this CIP must be submitted to the EC for approval (by the investigator or Sponsor, as applicable), as required by local procedures, and the approval documentation must be submitted to Sponsor before implementation.

13.0 Statistical Methods

. Subject data will be summarized using listings and tables. All critical electronic case report form data will be listed per subject for all enrolled subjects. For continuous variables, descriptive statistics will include, at a minimum, the number of observations, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects will be presented.

For all analyses, the baseline observation is defined as the last available measurement on or before the date of the implantation procedure.

13.1 Sample Size Justification

Based on the results presented in Section 3.4 for Version 1.3 of the WaveCrest device in the WAVECREST 1 study and during limited market release, a total of 7 (4.2%) subjects out of 165 implanted subjects have experienced an occurrence of the composite safety endpoint of all-cause mortality, pericardial effusion requiring intervention, device embolization from the LAA, device thrombus, or ischemic stroke. If the expected rate of occurrence of the composite safety endpoint is 5%, then a sample size of 56 subjects will result in the upper bound of a two-sided exact 95% confidence interval being less than 15% (a clinically and statistically significant difference from previous experience). Assuming a drop-out rate of ten percent, total enrollment in this study will be at least 63 subjects (56/0.9 rounded up).

13.2 Endpoint Analysis

The number and percentage of subjects experiencing an occurrence of the composite safety endpoint will be summarized at the 45-day time point. An exact 95% confidence interval will also be provided. Similar summaries will also be provided for the number of subjects in whom Device Success, Technical Success at implant, and Procedural Success are achieved. These summaries will be repeated at the completion of the study.

The number and percentage of subjects reporting adverse events will be summarized by MedDRA system organ class and preferred term. Separate summaries will also be provided for device-related AEs and procedure-related AEs. All serious adverse events (SAEs), device-related SAEs, and procedure-related SAEs will also be summarized by system organ class and preferred term. All adverse events occurring up to the 45-day time point and then all adverse events occurring through the completion of the study will be summarized separately.

Demographic and baseline characteristics, procedural data (duration of surgery, number of devices attempted, length of stay), medical history, and physical examinations, as well as other data collected during the study will also be presented.

14.0 Risk Evaluation

Coherex Medical has conducted a risk analysis to identify potential hazards associated with use of the WaveCrest device and to determine how to mitigate the risks. The risk analysis included a review of the Use Failure Mode and Effects Analysis (FMEA), Design FMEA, Process FMEA, and currently published literature. The anticipated clinical risks and benefits associated with the use of the WaveCrest device are described in the following sections.

14.1 Anticipated Clinical Benefits

Specific benefits that may be associated with percutaneous LAA occlusion include reduction of embolic events (including possible stroke or TIA), associated with thrombus formation in the LAA in patients with non-valvular atrial fibrillation.

In addition to these benefits, specific benefits that may be associated with use of the WaveCrest LAA Occlusion System compared to other devices used for LAA occlusion include:

- Ease of use due to ostial positioning
- Shorter procedure times
- Evaluation of closure at implant
- Reduced thrombus formation related to the device due to the selection of occluder materials
- Improved anchor position near the point of occlusion for improved stability
- Reduction in pericardial effusions due to absence of Sheath manipulation deep in the LAA tissue

14.2 Residual Risks

Risks involved with the use of the WaveCrest device have been mitigated to the extent possible in its design, non-clinical testing, and with the training and instructions given to clinicians for its use; however, all risks of a clinical procedure and implantable medical device cannot be mitigated. The residual risks of using the device are discussed in sections below.

14.3 Risks Associated with Participation in the Clinical Investigation

For subjects, the risks associated with participation in a post-market clinical investigation based on approved device use and indications are expected to be no different from those experienced in the commercial setting.

Potential adverse events specific to device placement include, but are not limited to:

- Device embolization, migration,misplacement or improper seal of the LAA
- Device failure, fracture or extrusion of device components
- Inability to recapture, reposition, or retrieve the device requiring surgical retrieval
- Thrombus formation on the device surface with the risk of subsequent embolization
- Tissue erosion
- Pericardial effusion requiring intervention and cardiac tamponade

Placement of the devices is performed using standard interventional cardiac catheterization techniques. Adverse events associated with these procedures include, but are not limited to:

- Air embolus
- Allergic reactions
- Anesthesia reactions
- Apnea
- Arrhythmia
- AV Fistula
- Blood loss requiring transfusion
- Cardiac perforation
- Contrast reaction
- Chest Pain
- Death
- Pulmonary vein obstruction
- Renal failure/insufficiency
- Scarring/venous thrombosis
- Stroke/transient ischemic attack
- Surgical Repair/Retrieval procedure
- Fever
- Hematoma/ecchymosis
- Hypertension; hypotension
- Infection including endocarditis
- Myocardial infarction
- Perforation of vessel or myocardium
- Pericardial effusion
- Pleural effusion
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolus
- Tamponade
- Thrombus formation/embolism
- Vagal reactions
- Valvular damage/insufficiency
- Vascular damage/ access site complications

14.4 Possible Interactions with Concomitant Medications

No interactions are expected between the WaveCrest device and concomitant medications.

Patients treated with the WaveCrest device will take, in due conformity with the approved device Instructions For Use, clopidogrel and aspirin for at least 90 days. The combination of these two medications may be associated with an increased risk of bleeding as compared to the risk when only one medication is used. Additional risks include:

- Internal bleeding
- Nose bleeds
- Bruising
- Prolonged bleeding from a cut or scrape
- Headache
- Upset stomach
- Nausea or vomiting
- Diarrhea
- Fever
- Skin rash
- Tissue death (necrosis)
- Decrease in white or red blood cells
- Inability to tolerate clopidogrel or aspirin
- Interaction with other medications or foods

14.5 Steps to be Taken to Control or Mitigate Risks

All of the adverse events listed in **Section 14.3** above are associated with percutaneous LAA occlusion and other percutaneous procedures. There are no additional potential adverse events specific to LAA closure with the WaveCrest device compared to existing LAA occlusion devices used for similar indications.

Many of the adverse events listed above mainly occurred when the device was: (1) not used as specified in the Instructions for Use (IFU); (2) used by unskilled/untrained operators; (3) used in a non-sterile environment; or (4) used past its expiration date. The IFU for the Coherex LAA Occlusion System provides clear instructions on how to use the device in a way that minimizes identified risks and notifies the user of potential harms.

Many risks associated with vascular interventional procedures are related to the condition of the patient and the patient's vasculature, coagulation, and renal systems, the patient's overall physical health, pre-existing medical conditions, and the clinician's overall skill level. These risks are minimized in this study by the specific requirements of cardiac anatomy as well as careful selection and training of clinicians.

14.6 Risk-to-Benefit Rationale

Based on a review of the Use, Design, and Process FMEAs, and based on the CE-mark approval of the device and its use within the approved indication the potential benefits of use of the WaveCrest device outweigh the risks.

14.7 Risk Management Procedures

Risks to subjects from participation in the study will be minimized by the following steps:

- Implanting investigators will be trained on the investigational device, the IFU, and the Clinical Investigation Plan prior to participating in the study. Retraining of investigators will be conducted if deviations from recommended use are noted.
- Subjects will participate in the study only upon providing consent and confirmation of meeting study eligibility criteria. Subjects will have follow-up visits according to the schedule specified in this CIP. Subjects participating in the study will receive antiplatelet and anticoagulation medications to minimize risk of thromboembolism.
- Adverse events and adverse device effects will be reported and monitored through the follow-up period and ECs will be notified per the local reporting requirements.
- Sites will be notified of unanticipated adverse device effects or other safety concerns that could negatively impact the safety of the subjects if such issues arise.
- Compliance of sites to the CIP and regulatory requirements will be monitored.
- The Medical Safety Officer will review the adverse events.

15.0 Publication Policy

Results of this clinical study may be submitted for publication without regard for whether the trial results are positive or negative. Sponsor will be responsible for oversight of the publication process and will have oversight of publications of results of the trial, the Physician Advisory Committee may advise.

Site-specific clinical study results may be published by Investigators in compliance with the Investigator Agreement and/or site agreement, as applicable.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

The study will be registered on the clinicaltrials.gov website and information will be updated on a regular basis as required.

16.0 Revision History

Rev.	Description of Change	Revised By	CO#	Effective Date
A	Initial Release	PPD		7 May 2015
B	Updated exclusion criteria to be consistent with IFU; minor edits			15 May 2015
C	Update to be consistent with latest version			08Feb2017

	of IFU, updated statistical section and latest internal study management decisions			

APPENDIX I: ACRONYMS AND DEFINITIONS

ACRONYMS

AF	Atrial Fibrillation
CIP	Clinical Investigational Plan
CT	Computed tomography
CRF	Case Report Form
EC	Ethics Committee
ePTFE	Expanded poly tetra fluoro ethylene
IFU	Instructions for Use
INR	International Normalized Ratio
IV	Intravenous
LAA	Left Atrial Appendage
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NYHA	New York Heart Association
PMCF	Post Market Clinical Follow-Up
QVSFS	Questionnaire for Verifying Stroke-Free Status
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist

DEFINITIONS

Atrial Fibrillation	
Paroxysmal	• AF that terminates spontaneously or with intervention within 7 days of onset • Episodes may recur with variable frequency.
Persistent	• Continuous AF that is sustained > 7 days.
Permanent	• Continuous AF that is sustained > 12 months that cannot or is not planned to be resolved with treatment • Note: For the purpose of this CIP, and for comparison to earlier LAA occlusion studies, permanent AF includes any subject with sustained AF ≥2 months without regard to ongoing treatment status.
Device Duration	Time from transseptal puncture to removal of delivery catheter
Device Embolization	A device that has dislodged from the Left Atrial Appendage and moved to a different cardiovascular structure
Device Migration	A device that has shifted from its original position to a different position in the Left Atrial Appendage post release
Procedure Duration	Time from venous puncture to removal of delivery catheter
Device Success	Device deployed and implanted in the correct position
Technical Success	• Occlusion of the LAA • No device-related complications • No leak >5mm on color Doppler TEE
Procedural Success	• Technical success • No procedure-related complications except uncomplicated (minor) device embolization (resolved by percutaneous retrieval during the procedure without surgical intervention or damage to surrounding cardiovascular structures)
Death	*VARC II Definition*[48]
Cardiovascular Death	Death that meets any of the following criteria: • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • Procedure-related death, including death related to complication of the procedure or treatment for a complication of the procedure • Valve-related death including structural or non-structural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause
Non-cardiovascular Death	Death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide)
Endocarditis	Fulfilment of the Duke endocarditis criteria [49] (see http://www.medcalc.com/endocarditis.html)
LAA Closure	No residual leak, or if leak is present no residual flow > 5mm on

	color Doppler TEE
Bleeding	*Bleeding Academic Research Consortium (BARC)*[50]*definition*
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to < 5g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop ≥ 5g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 units whole blood or packed red blood cells within a 48-hour period† Chest tube output ≥2L within a 24-hour period
Type 5	Fatal bleeding
Major Bleeding	Type 3 or greater as defined by *Bleeding Academic Research Consortium (BARC)*
Major Vascular Complication	Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment
Residual Gap	Space between the implanted device and adjacent LAA tissue. This gap is measured on TEE where there is high velocity color flow and a 2d image showing space between implant and tissue.
Stroke/TIA	
All Stroke	Any ischemic or hemorrhagic stroke
Ischemic Stroke	Sudden onset neurological deficit in a vascular territory thought to be due

	to cerebral or retinal ischemia that a) lasts longer than 24 hours or b) lasts less than 24 hours and is associated with a neuroanatomically relevant lesion on neuroimaging, or confirmed visualized retinal infarct. A global (rather than focal) deficit thought to be due to anoxic brain injury is also considered a stroke. Ischemic stroke with hemorrhagic transformation is also categorized here.
Hemorrhagic Stroke	Any atraumatic symptomatic intracerebral or subarachnoid hemorrhage.
TIA	Sudden onset neurological deficit in a vascular territory thought to be due to cerebral or retinal ischemia with resolution in less than 24 hours and without evidence of tissue injury on imaging or fundoscopic examination
Major Stroke	• Any change on the modified Rankin Scale score $\geq$ 2 points that persists at 30 days post-stroke
Minor Stroke	Does not meet definition of Major Stroke
Stroke of Cardioembolic Origin	*Using ASCOD Classification system*[51] Stroke will be considered cardioembolic *except* if there is: • Another "potentially causal" mechanism is identified (any of A1, S1, O1, D1), AND • The C grade is 0, 3, or 9 (unlikely since all patients have AF at implant)
Systemic Thromboembolism	Any acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic, surgical or autopsy evidence is required to show abrupt arterial occlusion.
Vulnerable Population	Individuals whose willingness to volunteer in a clinical study could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate Example: individuals with lack of or loss of autonomy due to immaturity or through mental disability, impoverished persons, prison population, and those incapable of giving consent.

APPENDIX II: CHA_2DS_2-VAsc Score

The CHA_2DS_2-VAsc Score is an ischemic stroke risk stratification method in subjects with non-valvular atrial fibrillation[16]. The score assigns 1 or 2 points for each of the following risk factors: Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes Mellitus, Prior Stroke or TIA or Thromboembolism, Vascular Disease, Age 65 to74 years, Female. The score ranges from a minimum of 0 to a maximum of 9, with lower scores having lower risk and higher scores having higher risk for ischemic strokes. Subjects in the study must have a minimum score of 2.

Stroke Risk Stratification with CHA_2DS_2-VAsc Score

Risk Factor	**Points**
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes Mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular Disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65 to 74 years	1
Female	1
Maximum Score	**9**

APPENDIX III: QUESTIONNAIRE FOR VERIFYING STROKE-FREE STATUS (QVSFS)

This questionnaire has 8 questions, as follows. At study follow-up visits, these questions need to be preceded by "Since your last study visit…":

1. Were you told by a physician that you had a stroke?
   □ Yes □ No

2. Were you told by a physician that you had a TIA, ministroke or transient ischemic attack?
   □ Yes □ No

3. Have you had a sudden painless weakness on one side of your body?
   □ Yes □ No

4. Have you had sudden numbness or a dead feeling on one side of your body?
   □ Yes □ No

5. Have you had sudden painless loss of vision in one or both eyes?
   □ Yes □ No

6. Have you suddenly lost one half of your vision?
   □ Yes □ No

7. Have you suddenly lost the ability to understand what people are saying?
   □ Yes □ No

8. Have you suddenly lost the ability to express yourself verbally or in writing?
   □ Yes □ No

QVSFS scores are obtained by giving 1 point to each "Yes" answer. The scores range from 0 (no questions positive) to 8 (all 8 questions positive).

Refer to Jones WJ, et al.[52] for further details.

APPENDIX IV: NEUROLOGIC ASSESSMENTS

Modified Rankin Scale

Refer to http://www.strokecenter.org/wp-content/uploads/2011/08/modified_rankin.pdf

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