# Clinical Investigational Plan for the WAVECREST 2 Trial

# Trial Title: WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2

A prospective, multicenter, randomized, active controlled, clinical trial of the Coherex WaveCrest® Left Atrial Appendage Occlusion System compared to the Watchman® LAA Closure Device for the reduction in risk of ischemic stroke or systemic embolism in subjects with non-valvular atrial fibrillation that have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation.

Document Date: 04-DEC-2019

**SPONSOR:**
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# INVESTIGATOR SIGNATURE PAGE

**Trial Name:** The WAVECREST 2 Trial

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**Protocol Number:** CHX_IP014

**IDE Number:** G170113

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**Sponsored by:** Coherex Medical, Inc.

I, the Undersigned,

Printed Name:_____

Title: _____

Address: _____

_____

_____

acting as an Investigator in the above-mentioned trial, undertake to perform the trial in due compliance with the present protocol and with all applicable Regulatory, Ethical and Good Clinical Practices requirements, including but not restricted to the Declaration of Helsinki, Code of Federal Regulations Title 21, and ISO14155.

No trial-specific tests or procedures will be undertaken prior to Institutional Review Board or Ethics Committee approval of the research and individual subject signature of an informed consent to participate in the trial. 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 and Food and Drug Administration requirements.

Signature: _____ Date: _____

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# 1. SYNOPSIS

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|---|---|
| Trial Title | WAVECREST 2 Trial: WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 |
| Name of Investigational Device | Coherex WaveCrest® Left Atrial Appendage Occlusion System |
| Purpose | To evaluate the safety and effectiveness of the Coherex WaveCrest Left Atrial Appendage Occlusion System |
| Intended Use | The Coherex WaveCrest Left Atrial Appendage Occlusion System is a percutaneous transcatheter device intended to be used for closure of the left atrial appendage (LAA) |
| Design | Prospective, multicenter, randomized, active control, clinical trial of the Coherex WaveCrest Left Atrial Appendage (LAA) device compared to the Watchman® LAA device for the reduction in risk of ischemic stroke or systemic embolism in subjects with non-valvular atrial fibrillation who have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation (OAC). |
| Blinding | The following personnel will be blinded to the randomization assignment and treatment received:<br>• Neurology personnel evaluating subject, to the extent possible<br>• Clinical Events Committee (CEC) that will adjudicate primary safety and effectiveness events, death (cardiovascular vs. non-cardiovascular), and bleeding category<br>• Investigator's staff administering the Questionnaire for Verifying Stroke-Free Status (QVSFS), the modified Rankin Scale (mRS), and the National Institutes of Health Stroke Scale (NIHSS) questionnaires |
| Devices Used | Watchman LAA Closure Device and Delivery Sheath<br>WaveCrest Left Atrial Appendage Occlusion System and Delivery Sheath |
| Subject Population | The subject population will include participants ≥ 18 years old diagnosed with non–valvular atrial fibrillation and a $CHADS_2$ score ≥ 2 or a $CHA_2DS_2$-VASc score ≥ 3 who have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation. |
| Definitions | See protocol definitions in **Appendix I: Acronyms and Definitions** |
| Primary Effectiveness Endpoint | Composite rate of ischemic stroke or systemic embolism at 24 months |
| Primary Safety Endpoint | Composite rate of:<br>• All cause death; or<br>• Procedure- or device-related complications requiring percutaneous or surgical intervention through 45 days post-procedure; or<br>• Major bleeding |

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| Secondary Endpoints | • Rate of ischemic stroke or systemic embolism with the WaveCrest device in comparison to the $CHADS_2$ and $CHA_2DS_2$-VASc imputed risk of ischemic stroke or systemic embolism in the absence of anticoagulant therapy<br>• Rate of LAA closure (gap ≤ 5mm) at 45 days |
| Descriptive Safety Endpoints | • Components of the composite primary safety endpoint through 45 days post-procedure<br>• The rates of stroke (all types) or pericardial effusion through 45 days post-procedure<br>• Pericardial effusion requiring surgical drainage through 7 days post-procedure or at hospital discharge, whichever is later<br>• Device- or procedure-related Serious Adverse Events (SAEs) reported by site at 45 days, 6 months, and at each annual follow-up period<br>• All-cause mortality 45 days, 6 months, and at each annual follow-up period<br>• Cardiovascular mortality at 45 days, 6 months, and at each annual follow-up period |
| Descriptive Effectiveness Endpoints | • Primary effectiveness endpoint event rate at 6 months, 1 year, 3 years, 4 years and 5 years<br>• Composite of all stroke, systemic thromboembolism, or TIA at 45 days, 6 months and at each annual follow-up period<br>• Landmark analysis of primary effectiveness endpoint from the 45-day visit to the time of each annual follow-up period<br>• Landmark analysis of the incidence of ischemic stroke from 6 months following device implantation and discontinuation of oral anticoagulant and dual antiplatelet therapy<br>• Composite of all-cause stroke at 45 days, 6 months, and at each annual follow-up period<br>• Incidence of thrombus on the surface of the device at 45 days, 1 year, and throughout all follow-up<br>• Strokes adjudicated as ischemic, hemorrhagic, or indeterminate at 45 days, 6 months, and at each annual follow-up period<br>• Strokes adjudicated as major or minor at 45 days, 6 months, and at each annual follow-up period<br>• Stroke adjudicated as cardioembolic in origin at 45 days, 6 months, and at each annual follow-up period<br>• Freedom from oral anticoagulants after each protocol-required follow-up visit<br>• Number of devices used per subject<br>• Procedural success |

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| | • Technical success<br>• Device success<br>• LAA Closure as determined by Echocardiography Core Lab (ECL) at 45 days, 6 months, and at 1 year<br>• Procedure time, device duration, contrast volume used, and fluoroscopy time |
| Inclusion Criteria | 1. Documented evidence of paroxysmal, persistent, or permanent non-valvular atrial fibrillation<br>2. At least 18 years of age<br>3. Calculated $CHADS_2$ score $\geq 2$ or $CHA_2DS_2$-VASc score $\geq 3$<br>4. Indication for warfarin therapy with an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation<br>5. Willing and able to comply with post-implant anticoagulation and antiplatelet regimen<br>6. Willing to participate in the required follow-up visits and tests<br>7. Subject has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board/Ethics Committee (IRB/EC) at the site |
| Exclusion Criteria | 1. Atrial fibrillation (AF) due to a reversible cause (e.g. thyrotoxicosis or post-operative)<br>2. Known contraindication and/or allergy to warfarin, nickel, aspirin, intravenous contrast, or P2Y12 inhibitors (clopidogrel, ticagrelor, and prasugrel), which cannot be adequately pre-medicated or desensitized<br>3. Conditions other than atrial fibrillation requiring long-term anticoagulation therapy<br>4. Contraindications to percutaneous catheterization procedures<br>5. Prior surgical LAA occlusion/exclusion or implanted with LAA occlusion device, or any prior attempt of such procedures<br>6. Prior percutaneous or surgical closure of a patent foramen ovale or atrial septal defect<br>7. Inability or unwillingness to take oral anticoagulation for 45 days post-procedure<br>8. New York Heart Association Class IV heart failure<br>9. Prior cardiac transplant, history of mitral valve replacement, or transcatheter mitral valve intervention, or any mechanical valve implant |

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| | 10. History of symptomatic carotid, intervertebral, or intracranial artery occlusion or stenosis without revascularization with the exception of known occlusion without symptoms > 6 months<br>11. Modified Rankin Scale Score ≥ 4<br>12. Chronic resting heart rate > 110 bpm<br>13. Congenital or other clinically significant cardiac anomalies requiring cardiac surgery or interventional repair<br>14. Stroke or transient ischemic attack (confirmed by Neurologist) within 60 days prior to enrollment<br>15. Myocardial infarction within 60 days prior to enrollment<br>16. Sepsis or any active infection requiring oral antibiotic therapy within 14 days or intravenous antibiotic therapy within 30 days prior to enrollment<br>17. Surgical or interventional cardiovascular and non-cardiovascular procedure including cardioversion within 30 days prior to enrollment or AF ablation within 60 days prior to enrollment or any planned general surgery or planned interventional procedure within 90 days after enrollment or any planned cardiac surgery<br>18. On renal replacement therapy, serum creatinine > 3.0 mg/dl (265 µmol/L) or calculated creatinine clearance < 25 ml/minute<br>19. Thrombocytopenia (<60,000 platelets/$mm^3$), leucopenia (white blood cell count < 3,000 cells/$mm^3$), or anemia (hemoglobin concentration < 10 gram/deciliter)<br>20. Any medical disorder or psychiatric illness that would interfere with successful completion of the trial<br>21. Currently participating in an investigational drug trial or another device trial that has not completed the primary endpoint (trials requiring extended follow-up for products that are commercially available are not considered investigational trials). Concurrent enrollment in the ACC LAAO Registry is permitted.<br>22. Subject belongs to a vulnerable population (see definition in **Appendix I: Acronyms and Definitions**)<br>23. Any condition that would reduce life expectancy to less than 2 years<br>24. Women of childbearing potential who are, or plan to become pregnant during the time of the trial (method of assessment per physician discretion) |
| Echocardiographic Exclusion Criteria | 1. Estimated left ventricular ejection fraction < 30%<br>2. Mitral valve stenosis defined as valve area < 1.5$cm^2$, mean gradient > 6mmHg, or any mitral valve deformity consistent with rheumatic valvular disease |

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| | 3. Aortic valve stenosis defined as valve area ≤1.0cm$^2$ or mean gradient >30mmHg<br>4. Circumferential pericardial effusion > 10mm, loculated pericardial effusion with the largest dimension > 10 mm, or symptomatic pericardial effusion of any size<br>5. Evidence of intracardiac thrombus (including in left atrial appendage, left ventricle or elsewhere)<br>6. Cardiac tumor or myxoma<br>7. Atrial septal defect that warrants closure<br>8. Complex atheroma in the ascending aorta or aortic arch as evidenced by mobile plaque.<br>9. Left Atrial Appendage size and shape are unsuitable for closure with a WaveCrest or Watchman device |
| Pre-Procedure Care | The following Baseline steps are recommended to be performed within 30 days **prior to** randomization but must be completed within 90 days **prior to** randomization (or within 90 days prior to treatment of roll-in subject):<br>• Document medical history (if not previously documented).<br>• Document appropriate rationale to seek a non-pharmacologic alternative therapy<br>• Perform physical exam<br>• Administer Quality of Life (QoL) SF-36 questionnaire<br>• Blood work to document CBC (HGB, WBC, platelets), and serum creatinine with INR and pregnancy as necessary<br>• $CHADS_2$ and $CHA_2DS_2$-VASc score (see **Appendix II** for calculation of $CHADS_2$ and $CHA_2DS_2$-VASc scores).<br>• Calculate HAS-BLED score (see **Appendix II** for calculation of HAS-BLED score)<br>• A trial staff member must administer the QVSFS to the subject (see **Appendix III).**<br>• All subjects must undergo NIHSS and mRS. Both must be administered by board-certified study Neurologist or trained and certified trial personnel (Appendix IV: Neurologic Assessments)<br>• If the subject has a history of stroke or TIA or if the baseline QVSFS score is > 0 the subject must be seen by a board-certified study Neurologist, including review of the following:<br>o Brain imaging (MRI unless contraindicated, then CT)<br>o If an imaging study is available following the prior stroke or TIA, a new study is not required per study Neurologist's discretion<br>o Completed NIHSS & mRS |

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| | • Perform baseline TEE. If thrombus is detected, the subject may undergo a 6-week course of anticoagulation followed by a repeat TEE. The subject may be re-evaluated after appropriate anticoagulation therapy and considered for device placement following documentation of absence of thrombus. The timeline from initial screening subject to the end of thrombus treatment must be treated within 90 days prior to randomization - or treatment, for roll-in subjects. |
| Post-Procedure Care | **Immediately post-procedure for 45 days post-implant:**<br>• All subjects must have a TTE to rule out pericardial effusion prior to discharge.<br>• Subjects receiving a Watchman device should begin/continue/resume warfarin therapy and aspirin per the product Directions for Use (DFU). [Note: Alternative vitamin K antagonists (e.g., acenocoumarol or phenprocoumon) may be used according to geographic standard of care.]<br>• Subjects receiving a WaveCrest device are required to start clopidogrel 75 mg daily and 75-100 mg aspirin daily starting 12-48 hours after the procedure (prasugrel or ticagrelor are allowable for clopidogrel intolerance, however, prasugrel is contraindicated in subjects with a history of prior stroke/TIA and both prasugrel and ticagrelor are contraindicated in subjects with a history of hemorrhagic stroke).<br><br>**45 days post-implant**<br>• At 45 days (+15/- 5 days) post-implant, a device assessment with TEE is to be performed.<br>• Warfarin cessation in the Watchman arm is per Watchman DFU but is recommended if peri-device flow by TEE is ≤ 5mm. If an adequate seal is not demonstrated, Watchman DFU recommendation for anticoagulation should be followed until peri-device flow ≤ 5mm is observed.<br>• When Watchman arm subjects stop warfarin, clopidogrel should be started per the product DFU.<br>• Evidence of device thrombus in either arm is recommended to be treated with a 6-week course of warfarin (+/- aspirin) and a repeat TEE. For subjects in the WaveCrest arm, clopidogrel should be stopped prior to initiating anticoagulation therapy.<br>• Subjects treated with the WaveCrest device with no evidence of device thrombus will continue dual antiplatelet therapy (DAPT) regardless of peri-device flow until 3 months post-implantation.<br><br>**3 months post-implant** |

<table>
<tr><td></td><td>

- WaveCrest arm subjects discontinuing clopidogrel (or P2Y12 inhibitor) must remain on 75-100mg aspirin daily indefinitely.

**6 months post-implant**

- Subjects with peri-device flow >5mm at 45 days will undergo a TEE at 6 months.
- Watchman arm subjects discontinuing warfarin and clopidogrel (or P2Y12 inhibitor) should take daily aspirin per the Watchman DFU indefinitely.

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<tr><td>Number of Trial Sites</td><td>Up to 100 sites will participate in the trial in North America, Europe, Australia, and Asia</td></tr>
<tr><td>Sample Size</td><td>

- Up to 1,550 subjects will be randomized in a 1:1 ratio between the WaveCrest and Watchman devices. The trial design offers at least 80% power to establish non-inferiority for the effectiveness and safety hypotheses across the range of possible event rates.
- Sites will be allowed up to 5 roll-in cases (up to 2 per operator) prior to randomization for a total of up to 500 roll-in subjects.
- Up to 2,050 total subjects will be enrolled

</td></tr>
<tr><td>Enrollment Phase</td><td>The enrollment phase is expected to last between 2 and 3 years.</td></tr>
<tr><td>Follow-up Evaluations</td><td>

***Office follow-up***: at 45 days, 6 months, 1, 2, 3, 4 & 5 years
***Phone follow-up***: at 3 month & 1.5, 2.5, 3.5, and 4.5 years
***Transesophageal echocardiograms (TEE)***:

- 45-day visit
- 6-month visit (*if LAA closure is not established at 45-day visit*)
- 1-year visit

**Summary of Study Assessments**

| ***Test*** | ***Screening /Baseline*** | ***Treatment*** | ***Discharge*** | ***Office F/U*** | ***Phone F/U*** |
|---|---|---|---|---|---|
| *Med Hx* | X | | | | |
| *Phys Exam* | X | X | X | X | |
| *Blood work* | X | | | | |
| *QVSFS* | X | | | X | X |
| *QoL* | X | | | X | |
| *Neuro eval* | X | X (*with stroke symptoms or QVSFS>0*)* | | | |
| *TEE* | X | X | | X* | |
| *TTE* | | | X | | |
| *AE eval* | X | X* | X | X | X |
| *Med review* | X | X | X | X | X |
| * - *see additional details in Table 4 of the CIP below* | | | | | |

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<tr><td>Echocardiography Core Lab</td><td>The echocardiography core lab will review all TTEs/TEEs performed at baseline, implant procedure (all echocardiographs), discharge, 45</td></tr>
</table>

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| | days, 6 months (if applicable), and 1-year follow-up as well as all TTEs/TEEs conducted during neurology evaluations for closure and thrombus and any TTEs/TEEs conducted at outside facilities (e.g., for adverse events). |
| Neurological Evaluations | • **At Baseline (after enrollment, prior to randomization or procedure for roll-in subjects):**<br>o Cerebrovascular and neurologic medical history (if not previously documented)<br>o QVSFS<br>o Quality of Life (QoL) questionnaire<br>o mRS/ NIHSS<br>o If subject has a history of a stroke/TIA or a baseline QVSFS score > 0, they must be seen by a board-certified study Neurologist to review the following:<br>▪ Brain imaging<br>- MRI preferred, CT if MRI contraindicated<br>- If an imaging study following the prior neurologic event is available, repeat imaging is not required per board certified Neurologist's discretion<br>▪ Completed NIHSS & mRS<br>• **At study office visits and phone follow-ups, or if the subject has an unscheduled visit for stroke symptoms:**<br>o Blinded trial personnel must administer QVSFS<br>o Subject-reported stroke/TIA or symptoms resulting in an increase in QVSFS **score > 0 since subject's most recent follow-up** require a visit with board-certified study Neurologist (an **Unscheduled Neurology Visit**) to review/perform the following:<br>▪ Completed mRS & NIHSS<br>▪ Brain imaging (MRI or CT if MRI is contraindicated)<br>▪ If stroke is confirmed, appropriate neurology-guided evaluation is indicated to determine stroke etiology, including the following recommended steps:<br>- Cervical/neck artery imaging (CTA/MRA/carotid Doppler)<br>- Intracranial artery imaging (CTA/MRA/transcranial Doppler)<br>- 24-hour cardiac monitoring<br>- TEE<br>- Subject must have a mRS re-administered 90 (+/- 15) days after any confirmed stroke |

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| | Note: Personnel who administer mRS & NIHSS must be certified, properly trained and blinded to subject randomization. |

## 1.1 Trial Flow Chart

***Screening:***
- Criteria that can be assessed prior to enrollment are reviewed
- Subject meets all assessable inclusion criteria
- Subject meets none of the assessable exclusion criteria

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***Enrollment:***
Subject provides informed consent to participate in the trial

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***Baseline:***
Study-specific assessments, including:
- Blood work & Physical Exam
- HAS-BLED score
- $CHADS_2$ & $CHA_2DS_2$-VASc scores
- QVSFS/QoL
- mRS/NIHSS
- TEE (within 90 days of randomization or procedure for roll-ins)
- Manage anticoagulation per section 6.2

↔

Subjects with Hx of stroke/TIA or QVSFS>0:
- Neurology exam
- Brain imaging (MRI, CT if MRI contraindicated)
  - Not required if imaging from event is available

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***Randomization:***
- Randomization ≤7-14 days prior to implant procedure

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***WaveCrest Treatment (Implant):***
- NOACs discontinued ≥ 24 hours pre-procedure
- Aspirin 75-100mg prior to procedure
- Routine (SOC) prophylactic antibiotic during implant
- Clopidogrel 75mg 12-48 hours post-procedure until 3 months post-implant
- Continue aspirin 75-100mg daily post-procedure

***Watchman Treatment (Implant):***
- NOACs discontinued ≥ 24 hours pre-procedure
- Routine (SOC) prophylactic antibiotic during implant
- Warfarin and aspirin should be managed per Watchman DFU

## 1.2 Trial Contacts

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### 1.3 Regulatory History

Coherex's WaveCrest device and Boston Scientific's Watchman device are both CE marked. The Watchman device is approved for commercial use in the United States by the FDA. The WaveCrest device is not approved for commercial use in the United States.

**The WAVECREST 2 Trial**

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|---|---|
| Trial Title | WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 |
| Investigational Device Exemption (IDE) Number | G150257 |
| Clinical Investigational Plan Number | CHX_IP014 |
| Revision Number | Rev H |
| Date | 04 December 2019 |

## 2. BACKGROUND AND JUSTIFICATION FOR CLINICAL TRIAL

This document is a Clinical Investigational Plan (CIP) for the WAVECREST 2 Investigational Device Exemption (IDE) trial. The WAVECREST 2 trial is a prospective, multicenter, randomized, active control, clinical trial to evaluate safety and effectiveness of the Coherex WaveCrest® Left Atrial Appendage (LAA) Occlusion System in subjects with non-valvular atrial fibrillation at increased risk for stroke or systemic embolism who have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation by demonstrating that the device is non-inferior to the Watchman® device with respect to the primary safety and effectiveness endpoints.

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 affecting an estimated 2.3 million individuals in the USA.[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 and non-valvular. 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 patients with AF although 90% of cases of paroxysmal AF are asymptomatic and therefore the prevalence may not be known. [5,6,7,8,9,10]

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.[16] AF accounts for one-fourth of all strokes in the elderly and is responsible for 70,000 strokes per year in the United States (AHA statistics). The risk of stroke in patients with non-valvular AF is approximately 5% per year in patients over age 76.[17] 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 patient populations.[18]

### 2.1 Oral Anticoagulant Therapy

Guidelines recommend chronic anticoagulation for patients with non-valvular AF at risk of stroke.[19,20,21] 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/permanent).[22,23,24,25,26] Despite its proven efficacy, warfarin is often not well tolerated by patients and has a 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,27,28] 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.[29] In a recent large national assessment of warfarin therapy use involving 138,319 subjects in the US and 2,683,674 INR results, the reported mean time in therapeutic range was only 53.7%.[30] Additionally, approximately 20% of patients with AF in whom

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

warfarin is recommended have a contraindication to warfarin (e.g., systemic or intracranial bleeding, potential for non-compliance with therapy, pregnancy, hypersensitivity).[31,32,33]

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.[34,35,36,37] 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.[38,39,40] This bleeding risk increases with age, decreased creatinine clearance and concomitant aspirin use. 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.

### 2.2 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[22,23,24,25,26] in subjects with non-valvular AF.[17] The resulting $CHADS_2$ scoring system[41] 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).[42] 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).[42] **Appendix II** explains the $CHADS_2$ and $CHA_2DS_2$-VASc scoring systems.

Table 1 shows stroke risks for the $CHA_2DS_2$-VASc scoring system.[19]

**Table 1: Adjusted Stroke Rate by CHA2DS2-VASc Score**

| $CHA_2DS_2$-VAsc Score | Adjusted Stroke Rate (% per year) |
|---|---|
| 0 | 0% |
| 1 | 1.3% |

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

Risk of bleeding may be assessed by the HAS-BLED score.[43] The score assigns 1 point for the presence of each of the following: hypertension, abnormal renal and/or liver function, previous stroke, bleeding tendency or predisposition, labile INRs, elderly and concomitant drugs and/or alcohol excess (**See Appendix II**). The score ranges from 0 to 9, with scores ≥ 3 indicating high risk of bleeding. HAS-BLED should not be used on its own to exclude patients from oral anticoagulant therapy; the score allows the clinician to identify bleeding risk factors and to correct those that are modifiable, e.g., by controlling blood pressure, removing concomitant antiplatelet or nonsteroidal anti-inflammatory drugs, and counseling the patient about reducing alcohol intake (if excessive).[41]

### 2.3 LAA Occlusion or Exclusion

As the LAA is the source of thrombi in more than 90% of non-valvular AF patients who experience stroke, there have been a number of developments in occlusion or exclusion of the LAA via surgical or percutaneous means.

### 2.4 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 largely limited to 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 of reducing the risk of thromboembolic events.[44] 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 subjects who underwent mitral valve replacement, ligation of the LAA was performed in 58 subjects.[45] After an average of almost six years, the incidence of an embolic event in subjects with LAA ligation was significantly lower than in subjects who underwent only mitral valve replacement (3% versus 17%, odds ratio 0.15, which fell to 0.08 if the subjects 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.[46,47,48] Surgical clips and ligation 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 subjects with chronic or intermittent AF.[49] 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.

### 2.5 Impetus for Percutaneous Approaches

Although the efficacy of 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, and 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 largely limited to 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 have reasons not to take chronic OAC. The recent EHRA/EAPCI expert consensus statement recognizes the role of catheter-based LAA occlusion, especially in patients who refuse OACs.[21]

### 2.6 Percutaneous LAA Occlusion Devices

**Table 2: Percutaneous LAA Closure Devices**

| Device Name, Manufacturer | Type of Device and Features |
|---|---|
| WaveCrest System,<br>Coherex Medical | Self-expanding nitinol frame with non-thrombogenic e-PTFE membrane and anchors to secure the device |
| WATCHMAN,<br>Boston Scientific | Self-expanding nitinol frame covered by a fabric that is permeable to blood and has sharp barbs to anchor the device |
| Amplatzer Cardiac Plug (ACP, Amulet),<br>St Jude Medical | Self-expandable nitinol device with fixation anchors |
| Lambre LAA Occlusion Device<br>Lifetech, Inc. (China) | Self-expandable nitinol device with fixation anchors |

A hybrid percutaneous device is the LARIAT (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 but does not have an approved indication for LAA closure. Because this device originally received regulatory approval as a ligation device, it is marketed as such; however, it is used for LAA closure as a means of reducing AF mediated stroke. There are other LAA occlusion devices currently in various stages of development.

#### Clinical Experience with Watchman Device

The largest body of clinical experience on the Watchman device is from the PROTECT-AF IDE trial, which randomized 707 subjects with non-valvular AF in a 2:1 ratio between intervention (i.e., Watchman device, n = 463) and control (i.e., warfarin, n = 244).[50] Subjects who received the intervention were required to be on warfarin for 45 days post-implant or until the LAA was closed followed by clopidogrel up to 6 months post-implant and aspirin indefinitely, whereas the control group was required to continue warfarin for the duration of follow-up. Effectiveness was assessed by a primary composite endpoint of stroke, cardiovascular death or systemic embolism. The trial was designed to demonstrate non-inferiority of the intervention to the control group. Trial participants were elderly (~72 years old) with approximately 70% having $CHADS_2$ score of $\geq 2$. At 1,065 subject-years of follow-up, the primary endpoint (composite of stroke, systemic embolism or cardiovascular death) event rate was 0.03 per subject-year in the intervention group and 0.049 per subject-year in the control group. The trial met its endpoint, demonstrating non-inferiority of the intervention. However, there was a higher rate of safety events (major bleeding, pericardial effusion, device embolization) in the intervention group than in the control group, primarily due to peri-procedural complications. Additionally, there were confounding effects of concomitant antithrombotic use and subjects not receiving the assigned treatment as randomized. The trial also enrolled some subjects who did not have a strong indication for warfarin ($CHADS_2$ score = 1). After 1,588 subject-years of follow-up, the primary effectiveness event rates remained lower in the intervention group (0.03 per subject-year) than the control group (0.043 per subject-year).[51] However, the rate of primary safety events remained higher in the intervention group than in the control group (0.055 versus 0.036 per subject-year). A second IDE trial (PREVAIL) was designed to study subjects at higher risk of stroke and excluded subjects who were not indicated for chronic clopidogrel therapy. The trial was designed with 2 co-primary effectiveness endpoints and 1 co-primary safety endpoint.[52] The trial enrolled subjects with a $CHADS_2$ score of $\geq 2$ or subjects with a $CHADS_2$ score of 1, who also had other risk factors for stroke (effectively $CHA_2DS_2$-VASc = 2). A total of 407 subjects were randomized (intervention: n = 269, control: n = 138). In a Bayesian analysis, the 18-month primary endpoint event (composite of stroke, systemic embolism or cardiovascular death) rates were 0.064 in the intervention group and 0.063 in the control group. The 18-month event rate for the second primary endpoint of ischemic stroke or systemic embolism beyond 7 days post-randomization occurred at a rate of 0.0253 subject-years in the intervention group and 0.020 in the control group. The third primary endpoint (composite of death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention) within 7 days of randomization occurred in 2.2% of subjects in the intervention group. The trial met two of the three primary endpoints (i.e., second and third primary endpoints). In a pooled subject-level meta-analysis combining the PROTECT AF and PREVAIL datasets (recently presented at an FDA Advisory Panel meeting[b]), the Watchman device was associated with:

- 21% reduction in the risk of the primary effectiveness endpoint (composite of stroke, systemic embolism or cardiovascular death) event,

[b] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm395638.htm

- reduced risk of disabling stroke (49%) relative to warfarin, and
- 27% relative reduction in the risk of all-cause mortality.

The analysis also revealed comparable rates of all-cause stroke or systemic embolism (hazard ratio 1.02) and warfarin was associated with an approximately 2-fold relative increase in the risk of major bleed.

### 2.7 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) subjects 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), **Version 1.3** (N=73). The study enrolled elderly subjects with an average $CHADS_2$ Score of 2.5 and at high risk of stroke. More than half (65%) of enrolled subjects were contraindicated for anticoagulation. Clinical results on device **Version 1.3** are as follows: procedural success was achieved in a majority of subjects (96%). Procedure duration averaged 68 minutes, with 47% requiring no device repositioning. On average, 1.3 devices were used (i.e., attempted) per subject. At 45 days, LAA closure, defined as residual gap ≤3mm, occurred in 97% of subjects. With LAA closure defined as a residual gap ≤5mm, LAA closure at 45 days was 100%. Pericardial effusions/tamponade occurred at a rate of 2.7%, none requiring surgical intervention, and there were no unanticipated adverse events or unanticipated adverse device effects.

The WaveCrest device received the CE Mark in August 2013 and was available commercially in Europe in October 2013. Procedural success was high during limited market release, with 88/92 (96%) successful implants as of July 2014. Pericardial effusions occurred at a rate of 3.3% (3/92). There was one device embolization (1.1%). In 2 subjects (2.2%), a thrombus was discovered on a follow-up TEE. There were no procedural strokes. In 2 subjects, there was damage to the inner liner of the sheath - both cases were "incidents" as defined by MEDDEV 2.12-1 Rev 8 and warranted a Field Safety Notice (FSN) and Field Safety Corrective Action (FSCA) in Aug 2014. A FSCA has resulted in modification to the Delivery Sheath liner. The device is described in **Section 5**. The related Change Notification was reviewed and approved July 29, 2015 and commercial use outside the United States resumed in September 2015.

### 2.8 Rationale to Conduct this Clinical Trial

The WAVECREST 2 trial is intended to evaluate the safety and effectiveness of Coherex's WaveCrest device in comparison with the Watchman device for the reduction in risk of ischemic stroke or systemic embolism in patients with non-valvular atrial fibrillation who are at increased risk for thromboembolism and have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation. The data from the trial will be used to support a pre-market approval (PMA) application of the WaveCrest device in the United States.

### 2.9 Justification for Choice of Control Arm

Boston Scientific's Watchman LAA occlusion device received PMA approval on March 13, 2015, to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or $CHA_2DS_2$-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

This trial will evaluate the safety and effectiveness of the Coherex WaveCrest device in comparison with the Watchman device which may become the standard of care in these high-risk patients.

# 3. RISKS AND BENEFITS OF THE CLINICAL TRIAL

The clinical investigation shall be conducted in accordance with the CIP. All parties participating in the conduct of the clinical investigation shall be qualified by education, training, or experience to perform their tasks and this shall be documented appropriately.

The clinical investigation shall not commence until the Sponsor receives written approval from the Institutional Review Board/Ethics Committee (IRB/EC)/Head of Medical Institution and relevant regulatory authorities, as applicable.

Sites will be selected for this trial based on the qualification and experience of the implanting Investigator, as well as commercial access to the Watchman device. [redacted] Site selection will also depend on the availability of experienced staff to conduct clinical research. The site will have Neurology personnel and/or other trial staff who are certified or trained to administer the modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), Questionnaire for Verifying Stroke-Free Status (QVSFS) and blinded to the subject's randomization assignment/device implanted to the extent possible.

## 3.1 Description of subject population

The subject population will include participants that are $\geq$ 18 years old diagnosed with non–valvular atrial fibrillation and a $CHADS_2$ score $\geq$ 2 or a $CHA_2DS_2$-VASc score $\geq$ 3 who have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation.

## 3.2 Anticipated clinical benefits

Subjects may not need to be on long-term warfarin therapy and thus will not be exposed to its associated complications.

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 subjects 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 **may** include:

- Enhanced LAA closure with ostial positioning
- Reduced thrombus formation on the atrial surface of the device due to the selection of occluder materials
- Improved anchor position near the point of occlusion for improved stability
- Reduction in pericardial effusions requiring surgery due to absence of sheath and device manipulation deep in the LAA tissue

### 3.3 Anticipated adverse events and adverse device effects

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/shortness of breath
- Arrhythmia
- Atrial septal defect
- AV Fistula
- Blood loss requiring transfusion
- Cardiac perforation
- Contrast reaction
- Chest pain
- Death
- Pulmonary vein obstruction
- Renal failure/insufficiency
- Respiratory failure/hypoxia
- Scarring/venous thrombosis
- Stroke/transient ischemic attack
- Surgical repair/retrieval procedure
- Fever
- Groin pain
- Hematoma/ecchymosis
- Hypertension; hypotension
- Infection and/or inflammation including endocarditis or pericarditis
- 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

This protocol requires TEEs, which may also result in adverse events including but not limited to the following:

- Bleeding
- Esophageal trauma
- Throat pain

The following items should be noted pertaining to potential adverse events:

- All of the adverse events listed 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 LAA Occlusion System compared to existing LAA occlusion devices used for similar indications.
- Many of the adverse events listed above are possible only if the device is: (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 subject and the subject's vasculature, the subject's overall physical health, pre-existing medical conditions, and the clinician's overall skill level. These risks are minimized in this trial by the specific requirements of inclusion/exclusion criteria and cardiac anatomy, as well as careful selection and training of clinicians.

### 3.4 Residual risks associated with the device under investigation, as identified in the risk analysis report

Coherex Medical has conducted a risk analysis to identify potential hazards associated with use of the WaveCrest LAA Occlusion System 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 LAA Occlusion System are described in the following sections.

### 3.5 Risks associated with participation in the clinical trial

For subjects randomized to the Watchman device, the risks associated with participation in the clinical investigation are expected to be no different from those experienced in the commercial setting. The methods of implantation are similar so the risks of participation in this clinical trial for subjects randomized to either the Watchman device or the WaveCrest device (**Section 3.3**) are expected to be similar.

### 3.6 Possible interactions with concomitant medical treatments and/or concurrent medical interventions

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

Oral anticoagulation is the standard of care to reduce the risk of stroke in people with atrial fibrillation. Subjects randomized to the Watchman arm should take post-implant medications

according to the product DFU. This includes warfarin for 45 days post-implant, DAPT through 6 months post-implant, and 300-325mg of aspirin indefinitely. Alternative vitamin K antagonists (e.g., acenocoumarol or phenprocoumon) may be used according to geographic standard of care. In the WaveCrest arm, subjects will receive clopidogrel (or ticagrelor or prasugrel) and aspirin for at least 3 months. The combination of these 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 warfarin or aspirin
- Interaction with other medications or foods

### 3.7 Steps that will be taken to control or mitigate the risks and study bias

To minimize potential clinical risks to subjects participating in this clinical trial and potential bias in the study:

- Investigators selected for this trial will not have significant equity interest in Johnson & Johnson (parent company of Coherex Medical). Physicians (or their spouses or dependent children) who receive compensation that could be affected by the outcome of this clinical trial or who have significant equity interest in Johnson & Johnson will not be selected as Investigators in this trial. Each Investigator will complete a financial disclosure form before subject enrollment, and as requested by the Sponsor during trial conduct and at the completion of the trial. A significant equity interest in Johnson & Johnson would include, for example:
    - Any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices;
    - an equity interest exceeding USD 50,000;
    - Significant payments of other sorts, which are payments that have a cumulative monetary value of more than USD 25,000, EXCLUDING the costs of conducting the trial or other clinical trials. This could include, for example, payments made to the individual or the institution to support activities (i.e., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria).

- Randomization will be stratified by site and $CHA_2DS_2$-VASc score ≤ 4 vs. > 4. To ensure the randomization ratio is maintained within lower enrolling sites, randomization will be assigned in permuted blocks within site, and sites will not be aware of the randomization schedule.
- The QVSFS must be administered at each follow-up interval (with the exception of the 3-month visit) by a person blinded to the subject's randomization/implanted device and post-implant medication regimen. The QVSFS can be administered in person, over the phone, and/or at satellite clinical locations. Blinding does not apply to baseline QVSFS administration. There is no special training required to administer this questionnaire. The **Signature and Delegation of Duties Log** may be used to indicate licensed hospital or clinic personnel who are blinded to the subject's randomization arm or device received to administer the questionnaire. Training of these personnel by the Sponsor will be documented in the **Training Log.**
- The mRS and NIHSS will be administered to all subjects at baseline, if an increase in QVSFS score is observed in a subsequent visit, or if a neurology office consultation is indicated. Blinding does not apply to baseline mRS/NIHSS. Any mRS or NIHSS during follow-up must be administered by a person blinded to the subject's randomization and implanted device, who has completed requisite training and is listed on the trial **Signature and Delegation of Duties Log** or appropriately documented.
- The board-certified study Neurologist who will assess the subject for primary endpoints will be blinded to the subject's randomization assignment and implanted device to the extent possible.
- An independent CEC will review and adjudicate events without knowledge of subject's randomization assignment or implanted device.
- Subjects may withdraw from the trial for any reason, either voluntarily or due to lost-to-follow-up. Adverse events will be reported through the date of subject discontinuation.

### 3.8 Risk-to-benefit rationale

Based on a review of the Use, Design, and Process FMEAs, the potential benefits of use of the WaveCrest LAA Occlusion System outweigh the risks. Percutaneous LAA occlusion may offer an alternative to physicians who are caring for subjects with AF who are at high risk for both bleeding and stroke.

## 4. PURPOSE

### 4.1 Name and Intended Use

The Coherex WaveCrest Left Atrial Appendage Occlusion System is a percutaneous transcatheter device intended to be used for closure of the left atrial appendage (LAA).

#### 4.1.1 Indications for Use

The Coherex WaveCrest Left Atrial Appendage Occlusion System is indicated in subjects who have all of the following:

- Non-valvular paroxysmal, persistent, or permanent atrial fibrillation
- LAA anatomy amenable to treatment by percutaneous techniques
- Risk factors for potential thrombus formation in the LAA

## 4.2 Scope of Trial

The WAVECREST 2 trial is a prospective, multicenter, randomized, active controlled, clinical trial to evaluate the safety and effectiveness of the Coherex WaveCrest Left Atrial Appendage (LAA) Occlusion System for the reduction in rate of ischemic stroke or systemic embolism in subjects with non-valvular atrial fibrillation who are at increased risk for stroke and have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation.

Subjects will be randomized in a 1:1 ratio to the Treatment Arm (Coherex WaveCrest LAA occlusion system) or the Control Arm (Boston Scientific's Watchman LAA occlusion system). Randomization will be stratified by site and $CHA_2DS_2$-VASc score $\leq 4$ vs. $> 4$. The trial is designed to demonstrate that safety and effectiveness of the WaveCrest device are non-inferior to the Watchman device. The subject, the implanting Investigator and catheterization laboratory staff will have knowledge of the assigned treatment. Trial personnel and the board-certified study Neurologist who will perform follow-up assessments for ascertainment of the primary effectiveness endpoint will be blinded to the randomization assignment and implanted device to the extent possible.

An independent Clinical Events Committee (CEC) will be blinded to the treatment assignment and will adjudicate protocol-defined events, including primary and secondary endpoints, death (cardiovascular vs. non-cardiovascular), and bleeding category. An independent Data Monitoring Committee (DMC) will monitor the safety of trial subjects and will review data at interim analyses. The DMC may provide recommendations for early regulatory filing of trial results upon review of interim analyses. An independent Echocardiography Core Laboratory (ECL) will review transesophageal echocardiograms (TEE) to assess LAA closure and device thrombus and will review post-stroke TEEs to ascertain the mechanism of stroke. Transthoracic echocardiograms (TTE) will be assessed by the core lab to assess for post-implant pericardial effusion.

### 4.2.1 Trial Size

Up to 1,550 subjects will be randomized and up to 500 subjects may be treated as roll-ins (total enrollment up to 2,050) at up to 100 investigational sites in North America, Europe, Australia and Asia. Up to 50% of subjects may be randomized outside the United States. Each investigational site may not randomize more than 15% of the total randomized subjects. Auxiliary sites (i.e., additional physical locations that are part of a clinical site) may be used to help in recruitment and follow-up activities but will not be utilized for protocol-specific assessments (e.g., subject consent, TEE, QVSFS, QoL, Neurological assessment, etc.), which will be performed only by sites that have been properly trained and have obtained the required IRB/EC approvals to conduct study-specific activities.

### 4.2.2 Duration

Enrollment is expected to last between 2 and 3 years, and the maximum follow-up duration is 5 years, for a total possible trial duration of approximately 8 years.

## 4.3 Endpoints

### 4.3.1 Primary Endpoint

This trial is designed to evaluate the safety and effectiveness of the Coherex WaveCrest LAA occlusion device to the Boston Scientific Watchman LAA occlusion device by demonstrating that the device is non-inferior to the Watchman Device with respect to the primary safety and effectiveness endpoints. If non-inferiority is demonstrated, superiority will be evaluated.

- The primary effectiveness endpoint is the composite rate of ischemic stroke or systemic embolism at 24 months.
- The primary safety endpoint is the composite rate of all cause death; procedure- or device-related complications requiring percutaneous or surgical intervention, including embolization of a LAA closure device, drainage of pericardial effusion, or repair of cardiac or vascular structures through 45 days post-procedure; or major bleeding.

### 4.3.2 Secondary Effectiveness Endpoints

- Rate of LAA closure, defined as a gap of ≤ 5mm as assessed by TEE, at 45 days
- Incidence of ischemic stroke or systemic embolism with the WaveCrest device in comparison to the $CHADS_2$ and $CHA_2DS_2$-VASc imputed risk of ischemic stroke or systemic embolism in the absence of anticoagulant therapy. No claims will be made on this endpoint.

## 4.4 Inclusion and Exclusion Criteria

### 4.4.1 Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be considered eligible for the clinical trial.

1. Documented evidence of paroxysmal, persistent, or permanent non-valvular atrial fibrillation
2. At least 18 years of age
3. Calculated $CHADS_2$ score ≥ 2 or $CHA_2DS_2$-VASc score ≥ 3 (See **Appendix II** for calculation of $CHADS_2$ and $CHA_2DS_2$-VASc scores)
4. Indication for warfarin therapy with an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation
5. Willing and able to comply with post-implant anticoagulation and antiplatelet regimen
6. Willing to participate in the required follow-up visits and tests
7. Subject has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB/EC at the site

### 4.4.2 Exclusion Criteria

If ANY of the following clinical exclusion criteria is met, the subject must be excluded from the clinical trial.

1. Atrial fibrillation (AF) due to a reversible cause (e.g. thyrotoxicosis or postoperative)
2. Known contraindication and/or allergy to warfarin, nickel, aspirin, intravenous contrast or P2Y12 inhibitors (clopidogrel, ticagrelor, and prasugrel), which cannot be adequately pre-medicated or desensitized
3. Conditions other than AF requiring long-term anticoagulation therapy
4. Contraindications for percutaneous catheterization procedures
5. Prior surgical LAA occlusion/exclusion or implanted with LAA occlusion device, or any prior attempt of such procedures
6. Prior percutaneous or surgical closure of a patent foramen ovale or atrial septal defect
7. Inability or unwillingness to take oral anticoagulation for 45 days post-procedure
8. New York Heart Association (NYHA) Class IV heart failure
9. Prior cardiac transplant, history of mitral valve replacement or transcatheter mitral valve intervention, or any mechanical valve implant
10. History of symptomatic carotid, intervertebral, or intracranial artery occlusion or stenosis without revascularization with the exception of known occlusion without symptoms > 6 months
11. mRS score ≥ 4
12. Chronic resting heart rate ≥ 110 bpm
13. Congenital or other clinically significant cardiac anomalies requiring cardiac surgery or interventional repair
14. Stroke or transient ischemic attack (confirmed by Neurologist) within 60 days prior to enrollment
15. Myocardial infarction within 60 days prior to enrollment
16. Sepsis or any active infection requiring oral antibiotic therapy within 14 days or intravenous antibiotic therapy within 30 days prior to enrollment
17. Surgical or interventional cardiovascular and non-cardiovascular procedure including cardioversion within 30 days prior to enrollment or AF ablation within 60 days prior to enrollment or any planned general surgery or interventional procedure within 90 days after enrollment or any planned cardiac surgery.
18. On renal replacement therapy, serum creatinine > 3.0 mg/dl (265 µmol/L) or calculated creatinine clearance < 25 ml/minute
19. Thrombocytopenia (<60,000 platelets/$mm^3$), leucopenia (white blood cell count < 3,000 cells/$mm^3$), or anemia (hemoglobin concentration < 10 grams/deciliter)
20. Any medical disorder or psychiatric illness that would interfere with successful completion of the trial
21. Currently participating in an investigational drug trial or another device trial that has not completed the primary endpoint (trials requiring extended follow-up for products that are commercially available are not considered investigational trials). Concurrent enrollment in the ACC LAAO Registry is permitted.

22. Subject belongs to a vulnerable population (see definition in **Appendix I: Acronyms and Definitions**)
23. Any condition that would reduce life expectancy to less than 2 years
24. Women of childbearing potential who are, or plan to become pregnant during the time of the trial (method of assessment per physician discretion)

### 4.4.3 Echocardiographic Exclusion Criteria

The following echocardiographic exclusion criteria must be assessed prior to randomization (or prior to the procedure for roll-in cases). The transesophageal echocardiogram (TEE) must be performed up to 90 days before, including just prior to, randomization (or the procedure for roll-in cases). If ANY of the following echocardiographic exclusion criteria is met, the subject must be excluded from the clinical trial.

1. Estimated left ventricular ejection fraction < 30%
2. Mitral valve stenosis defined as valve area < 1.5cm$^2$, mean gradient > 6mmHg, or any mitral valve deformity consistent with rheumatic valvular disease
3. Aortic valve stenosis defined as valve area ≤1.0cm$^2$ or mean gradient >30mmHg
4. Circumferential pericardial effusion > 10mm, loculated pericardial effusion with largest dimension > 10mm, or symptomatic pericardial effusion of any size
5. Evidence of intracardiac thrombus
6. Cardiac tumor or myxoma
7. Atrial septal defect that warrants closure
8. Complex atheroma in the ascending aorta or aortic arch as evidenced by mobile plaque
9. Left Atrial Appendage size and shape are unsuitable for closure with a WaveCrest or Watchman device

### 4.4.4 Adequate Representation of Women and Minorities

Historically, women have been underrepresented in or excluded from many clinical studies, leading to lack of information for women and their physicians regarding the risks and benefits of many medical treatments and diagnostic procedures. It is the Sponsor's intent to apply the principles from FDA's guidance titled Evaluation of Sex-Specific Data in Medical Device Clinical Studies in the WAVECREST 2 trial to ensure adequate representation of women and minorities.

Atrial fibrillation affects 1-2% of the population. The prevalence of atrial fibrillation increases with age, from < 0.5% at 40-50 years, to 5-15% at 80 years, with men being affected more often than women.[20] Consistent with this, several clinical studies on LAA closure devices to date (PROTECT-AF, PREVAIL and WAVECREST 1) enrolled an elderly cohort (average age ~72 years) with approximately one-third being women. As the WAVECREST 2 trial will enroll subjects with $CHA_2DS_2$-VASc score ≥ 3 (which gives a minimum score of 1 for women), the proportion of women in this trial is expected to be larger than one-third. Thus, women are expected to be adequately represented in the WAVECREST 2 trial.

In addition, the Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in the WAVECREST 2 trial:

- Where possible, sites will be selected where recruitment of women and racial or ethnic minorities can be more easily facilitated.
- Sites will be instructed to screen all subjects who have documented non-valvular atrial fibrillation and reasons to avoid chronic OAC, without regard to sex or race.
- If allowed by national regulations, sites will offer nominal reimbursement to trial participants for protocol-required office follow-up visits, as laid out in the Clinical Trial Agreement with the Sponsor.

Statistical analyses of the primary effectiveness and safety endpoints will be carried out to evaluate any interaction effect between treatment (WaveCrest or Watchman) and gender.

## 4.5 Subject Population

### 4.5.1 Subject Screening

Sites may begin screening subjects for the trial upon receiving IRB/EC approval to initiate the trial. Prior to enrollment in the trial, site personnel shall evaluate any potential candidates by reviewing the patient's medical records against the inclusion and exclusion criteria and interviewing the candidate subject. Assessment for trial eligibility may be based on patient's medical records at the site and interview with a candidate subject. Potential subjects will be asked to complete the informed consent process.

### 4.5.2 Point of Enrollment

Subjects will be considered enrolled and followed from the time an informed consent form is signed. Subjects will be documented as a roll-in subject, a randomized subject, or a screen failure**.** Enrolled screen failures will be excluded from the randomized cohort. Any adverse events in these subjects will be documented in eCRFs**.** Intent-to-treat will be established when they have completed screening, met all inclusion criteria, none of the exclusion criteria, and are randomized.

### 4.5.3 Enrollment of Medicare Beneficiaries (*US Subjects Only*)

This clinical trial will enroll Medicare beneficiaries and therefore conforms to all standards of Medicare coverage requirements. Risks and benefits of the clinical trial section describe how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

Subjects enrolled in the clinical trial are expected to be consistent with the Medicare population based on age and as such, the trial results are expected to be applicable to the general Medicare population.

### 4.5.4 Vulnerable Population

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

### 4.5.5 Description of the specific informed consent process

All IRB/ECs must comply with applicable regulations (21 CFR 56) and IDE regulations (21CFR 812) and/or appropriate international standards (ISO 14155:2011) in reviewing and approving investigational device documents and processes. The informed consent process must be appropriately documented in compliance with IRB/EC approval conditions and applicable local regulatory requirements.

### 4.5.6 Responsibilities

An IRB/EC shall safeguard the rights, safety, and well-being of all trial subjects.

### 4.5.7 Composition

The IRB/EC shall be composed of members meeting the minimum requirements set forth in 21 CFR 56.107 and/or any other applicable regulatory requirements.

### 4.5.8 Initial IRB/EC Approval

Prior to shipment of investigational devices for this trial, the Sponsor will require documentation of IRB/EC approval of the CIP and any information used in the subject informed consent process.

### 4.5.9 Annual IRB/EC Renewal

An IRB/EC shall conduct continuing review of the clinical trial at intervals appropriate to the degree of risk posed by the device, but not less than once per year (per applicable regulations).

## 4.6 Informed Consent

### 4.6.1 General Process

All subjects must sign and date the IRB/ EC approved informed consent prior to undergoing any trial-specific tests, assessments or procedures. The Investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical trial that are relevant to the subject's decision to participate in the clinical trial. The Investigator or his/her authorized designee who have been trained on the protocol will explain the nature and scope of the trial, potential risks and benefits of participation. Trial personnel must explain that agreeing to participate in the trial and signing an informed consent form does not guarantee trial participation.

The subject must be provided ample time to read and understand the informed consent form and to consider participation in the clinical trial. If the subject agrees to participate, the informed consent form must be signed and dated by the subject. The person obtaining informed consent must sign, date and time the informed consent prior to conducting any trial-specific tests, assessments or procedures. Additional site personnel may be required by the site's IRB/EC to sign the informed consent form. 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.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's IRB/EC. Failure to obtain

informed consent from a subject prior to undergoing any trial-specific tests, assessments, or procedures should be reported to the Sponsor within 5 working days and to the reviewing center's IRB/EC consistent with the center's IRB/EC reporting requirements.

Subject information may be entered only after the subject has provided informed consent. Subjects who are informally reviewed by the Investigator for inclusion in the trial but do not meet trial criteria and do not sign an Informed Consent will not be tracked.

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) or as required per local regulations. Subject confidentiality will be maintained throughout the clinical trial 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 trial may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

The informed consent for US subjects only will also request authorization for release of billing information specific to the subject's participation in the study. Specifically, the cost and frequency of health care utilization for the study procedure as well as any additional hospitalizations during the study period will be collected. This information will not be reported to the Food and Drug Administration as part of the IDE reporting. The hospitalization healthcare data to be collected will include but is not limited to: copies of the subject's hospital bills (UB04) and/or any itemized hospital bills for services. Data to be collected from the UB04 or itemized patient bill includes: Subject admission date, discharge date, procedure date, ICD-10 diagnosis codes, ICD-10 procedure codes, DRG assignment, and total charges for the hospitalization by revenue center. The Sponsor will also collect health economic data associated with any follow up care for the duration of the study including any medical procedures, ER visits, or outpatient visits to address issues related to stroke or cardiovascular conditions. All forms must be de-identified prior to submission to the Sponsor.

Sites may offer nominal reimbursement for their subjects for office follow-up visits required per this CIP, if allowed by national regulations, as laid out in the Clinical Trial Agreement with the Sponsor.

### 4.6.2 Informed consent will be obtained in Subjects unable to read or write

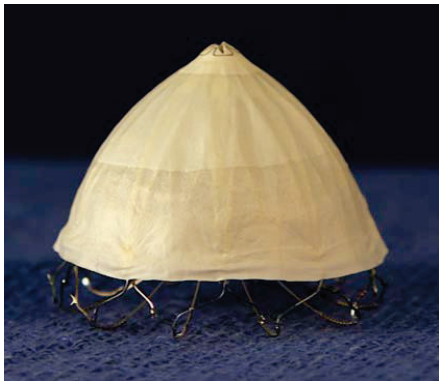
Informed consent will be obtained through a supervised oral process if a subject is unable to read or write. An independent witness will be present throughout the process. The written informed consent form and any other information will be read aloud and explained to the prospective subject and, whenever possible, either will sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

# 5. DEVICE UNDER INVESTIGATION AND CONTROL COMPARATORS

## 5.1 Device Description

The Coherex WaveCrest Left Atrial Appendage Occlusion System ("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 thrombus and tissue growth.

**Figure 1: Coherex Left Atrial Appendage Implant**



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. Anchoring and occlusion can then be assessed by TEE. When anchoring and occlusion are confirmed, the implant is detached and left within the LAA. The WaveCrest device implant is available in diameter sizes of 22, 27 and 32 mm.

**Devices:**

| Coherex Catalog Number (EU) | Coherex Catalog Number (US/AUS) | Coherex Catalog Number (China) | Implant Size |
|---|---|---|---|
| 1503 | 2503 | 3503 | 22mm |
| 1513 | 2513 | 3513 | 27mm |
| 1523 | 2523 | 3523 | 32mm |

**Delivery Sheaths:**

| Coherex Catalog Number (EU) | Coherex Catalog Number (US/AUS) | Coherex Catalog Number (China) | Name | Description |
|---|---|---|---|---|
| 1530 | 2530 | 3530 | 60 | 60° distal curve |
| 1540 | 2540 | 3540 | 75 | 75° distal curve |
| 1541 | 2541 | 3541 | 90 | 90° distal curve |
| 1551 | 2551 | 3551 | 90s | 90° distal curve with superior tip angle |

### 5.2 Control device (Watchman LAA Occlusion System)

The Watchman Left Atrial Appendage Closure (LAAC) System ("Watchman Device") is intended to reduce the risk of thromboembolism from the left atrial appendage (LAA) in subjects with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or $CHA_2DS_2$-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The Watchman device is intended for percutaneous, transcatheter closure of the left atrial appendage and consists of the Watchman Access System (Access Sheath and Dilator) and Watchman Delivery System (Delivery Catheter and Watchman Device). The Access Sheath and Delivery Catheter permit device placement in the left atrial appendage (LAA) via femoral venous access and inter--atrial septum crossing into the left atrium. The Watchman Device is a self-expanding nitinol structure with a polyethylene terephthalate (PET) porous membrane on the proximal face. The device is constrained within the Delivery System until deployment into the LAA.

The device is available in five sizes from 21 to 33 mm. Appropriate device sizing is determined by LAA measurements using fluoroscopy (fluoro) and transesophageal echocardiography (TEE).

The Watchman Device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to close the appendage to inflow. The placement procedure can be done under local or general anesthesia in a hospital cardiac catheterization or electrophysiology laboratory setting.

Newer generations of the Watchman device approved by the FDA for use in the US or approved at sites outside the US where the trial is being conducted may be used in the Control Arm if they become commercially available during the trial.

### 5.3 Device Accountability

Investigational devices will be shipped by the Sponsor to approved investigational sites after Sponsor receipt of the IRB/EC approval letter, signed Investigator Agreement and Clinical Trial Agreement and documentation of online device training. Implant procedures will not be performed until Site Initiation and device training have been completed. Product received at investigational sites will be logged into a **Device Tracking and Disposition Log** which may be part of the electronic data collection system. Investigators must reconcile and retain disposition documentation including the date of receipt, the identification of each investigational device (batch number, serial number or unique code), the subject identification, the date of use, the location and the expiration date and final disposition. Throughout the course of the trial, the **Device Tracking and Disposition Log** will be used to track the disposition of investigational devices, and clinical monitors will review the log and verify against trial records and existing inventory at the site. Access to investigational devices shall be controlled, and investigational devices shall be used only in the clinical investigation, according to this CIP, in accordance with Sponsor procedures, and in compliance with applicable federal and local regulations. Investigators and trial personnel shall be trained to Sponsor procedures on device accountability.

Coherex Medical will also maintain device accountability documenting all shipments and returns of investigational devices.

Sites with access to commercially available WaveCrest devices will be allowed to use those devices and will not be required to adhere to Investigational Device accountability as described above. Information regarding any commercially available WaveCrest product used in procedures will be recorded in the same manner as Investigational product.

### 5.4 Device Handling and Storage

Coherex Medical requires all investigational products to be stored according to the labeling, in a secure area to prevent unauthorized access or use. This will prevent non-investigational use of products that are provided for this trial. In some countries, commercial product that is identical to the Investigational Device will be used in the study and therefore does not require limited access.

## 6. PROCEDURES

The clinical trial will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical trial will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

### 6.1 Baseline Evaluation and Randomization/Roll-in

The Baseline time period begins with subject enrollment (informed consent) and ends with either vascular access in the interventional procedure (roll-in subjects) or randomization (randomized subjects). [redacted] Sites must receive approval from Sponsor to begin implantation procedures. This approval should be retained in the site regulatory binder. Sponsor personnel must be present for all roll-in procedures. Once a site begins randomizing subjects in the trial ("randomization phase"), no roll-in subjects will be permitted for that site.

All subjects are considered enrolled when the Informed Consent is signed. Standard of care tests or assessments may be used to evaluate Inclusion and Exclusion Criteria if the test or assessment meets the requirements of this CIP.

The following Baseline steps are recommended to be performed within 30 days **prior to** randomization but must be completed within 90 days **prior to** randomization (or within 90 days prior to treatment of roll-in subject):

- Document medical history (if not previously documented).
- Document appropriate rationale to seek a non-pharmacologic alternative therapy
- Perform physical exam
- Administer Quality of Life (QoL) questionnaire (see **Quality of Life Questionnaire - SF-36**).
- Blood work to document CBC (HGB, WBC, platelets), serum creatinine with INR and pregnancy (as necessary)
- $CHADS_2$ and $CHA_2DS_2$-VASc score (see **Appendix II** for calculation of $CHADS_2$ and $CHA_2DS_2$-VASc scores).
- Calculate HAS-BLED score (see **Appendix II** for calculation of HAS-BLED score)
- A trial staff member must administer the QVSFS to the subject (see **Appendix III: Questionnaire for Verifying Stroke-Free Status).**
- All subjects must undergo a NIHSS and a mRS. Both must be administered by board-certified study Neurologist or trained and certified trial personnel (Appendix IV: Neurologic Assessments)
- If the subject has a history of stroke or TIA or if the baseline QVSFS score is > 0 the subject must be seen by a board-certified study Neurologist, including review of the following:
  - Brain imaging (MRI unless contraindicated, then CT)
    - NOTE: If an imaging study is available following the prior stroke or TIA, a new study is not required per study Neurologist's discretion
  - Completed NIHSS and mRS.

- Perform baseline TEE. If thrombus is detected, the subject may undergo a 6-week course of anticoagulation followed by a repeat TEE. The subject may be re-evaluated after appropriate anticoagulation therapy and considered for device placement following documentation of absence of thrombus. The timeline from initial screening to the end of thrombus treatment must be within 90 days prior to randomization - or treatment, for roll-in subjects.
- Ensure adequate supply of Watchman and WaveCrest devices are available in inventory
- Notify Sponsor of upcoming randomization (or roll-in) procedure and potential implant dates to ensure adequate time for Sponsor to organize case support in order to meet the timelines required per this Clinical Investigation Plan. Sponsor personnel will be present at each WaveCrest implant procedure to provide clinical support to the Investigator regarding instructions for use and procedural steps during the procedure. Sponsor personnel may help ensure all data required per this CIP are collected but will not interpret or record any data in trial documents.

Once these tasks have been completed, subjects will be randomized using the study EDC system. If the baseline TEE is performed immediately prior to the procedure, then randomization must take place as soon as the baseline TEE is completed, and the subject is deemed to meet none of the echocardiographic exclusion criteria.

If the site requires case support for subjects randomized to the Watchman device, arrangements must be made with appropriate company personnel prior to randomization in order to meet the timelines required per this CIP.

For randomized subjects, the subject will be randomized through the database upon completion of required elements of the **Baseline Visit** and required entries in the database. Designated trial personnel will be notified of the device assignment (WaveCrest or Watchman) to which the subject has been randomized.

Echocardiographic screening for roll-in subjects may be performed on the same day as the planned implant procedure provided the echocardiogram is completed prior to initiating vascular access. The subject may be treated only if the subject continues to meet all Inclusion and none of the Exclusion criteria (**Section 4.4)**.

### 6.2 Treatment Visit

For roll-in subjects, the Treatment Visit is recommended to occur within 90 days of enrollment and occurs upon initiation of vascular access for the purpose of the WaveCrest implant.

For randomized subjects, the Treatment Visit is recommended within 7 days of randomization, but in all cases must occur within 14 days of randomization. At this visit, the randomized subject will undergo the WaveCrest or Watchman device implant procedure, as randomized. Absence of intracardiac thrombus must be confirmed by TEE prior to starting the implant procedure. If thrombus is detected, it is recommended the subject undergo a 6-week course of anticoagulation followed by a repeat TEE. The subject may be re-evaluated after appropriate anticoagulation therapy and considered for device placement following documentation of absence of thrombus. The subject will remain in the same arm of the trial to which they were originally randomized and receive the same follow-up.

**Pre-Procedure Medications**

- **Anticoagulation Therapy**
  If the subject has been on direct oral anticoagulation (DOAC) therapy, medication should be stopped at least 24 hours prior to the implant procedure (following manufacturer's guidelines for use) in both arms.
  - *WaveCrest arm*: Subjects currently taking warfarin should suspend its use 3 days prior to the implant procedure. It is recommended but not required that the subject's INR be <2.0 prior to the implant procedure. Warfarin may be discontinued less than 3 days prior to the implant procedure when the Investigator deems discontinuation to pose a significant risk to the subject (e.g., select subjects with a history of prior stroke or LAA thrombus, or a high $CHA_2DS_2$-VASc score). Within 24 hours of the implant procedure, 75-325mg aspirin should be administered.
  - *Watchman arm*: Warfarin and aspirin use should be managed according to the Watchman DFU.
  - If randomization will take place <3 days prior to the implant procedure, subjects taking warfarin pre-procedure should stop its use 3 days prior to the implant procedure. Warfarin may be discontinued less than 3 days prior to the implant procedure when the Investigator deems discontinuation to pose a significant risk to the subject (e.g., select subjects with a history of prior stroke or LAA thrombus, or a high $CHA_2DS_2$-VASc score).
- **Antibiotic Therapy**
  Immediately before the implant procedure, the subject should receive routine prophylactic antibiotics per the site's standard of care

## 6.3 Implant Procedure

Follow the Coherex WaveCrest LAA Occlusion System or the Boston Scientific Watchman LAA Occlusion System IFU/DFU, as applicable, for the implant procedure. [redacted]

4. [redacted]

Record the following information:

- Date of procedure, catheterization laboratory entry/exit time, procedure duration (see **Appendix I: Acronyms and Definitions**), device duration (see **Appendix I: Acronyms and Definitions**), device model number and serial number, date of implant, number of devices used, fluoroscopy and contrast volume used
- Warfarin and aspirin should be administered to Watchman arm subjects according to the product DFU. Per site/geographic standard of care, alternative vitamin K antagonists (e.g., acenocoumarol or phenprocoumon) may be used.
- Administer clopidogrel 75 mg to WaveCrest arm subjects within 12-48 hours, then daily post-procedure (prasugrel or ticagrelor are allowable for clopidogrel intolerance, however, prasugrel is contraindicated in subjects with a history of prior stroke/TIA and both prasugrel and ticagrelor are contraindicated in subjects with a history of hemorrhagic stroke). Administer aspirin (75-100 mg) within 24 hours, then daily post- procedure.
- Collect TEE/ICE images and submit images to ECL
- [redacted].
- Record cardiac medications, including antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations.

## 6.4 Discharge

Before the subject is discharged from the hospital:

- Record adverse events, device malfunctions, and protocol deviations as appropriate
- If there is any concern for stroke, a Neurologist, blinded to subject's randomization and implanted device to the extent possible, must evaluate the subject before discharge. (See **Section 6.12** for details of Unscheduled Neurology Visit)
- Record cardiac medications, including antiplatelet and anticoagulant medications
- Watchman subjects should be discharged on warfarin and aspirin per the Watchman DFU. For subjects on dual antiplatelet therapy, who will also require warfarin, it is recommended that INR be targeted to 2.0-2.5.
- Discharge WaveCrest subjects on 75-100 mg aspirin daily and clopidogrel (prasugrel or ticagrelor are allowable for clopidogrel intolerance, however, prasugrel is contraindicated in subjects with a history of prior stroke/TIA and both are contraindicated in subjects with a history of hemorrhagic stroke).
- Table 3 summarizes the post-procedure anticoagulation and antiplatelet regimen for the duration of the trial.
- A physical exam (vital signs at a minimum) must be done prior to discharge.

- A transthoracic echocardiogram (TTE) must be performed on all subjects to rule out a pericardial effusion prior to discharge.

**Note:** Subjects who are not implanted with a device must NOT undergo any additional LAA closure procedure with any device within 45 days of the initial implant procedure, except as randomized. At the discretion of the investigator, a second attempt to implant a subject as randomized may be made if there is reasonable medical justification to make such an attempt that is approved in writing by the Sponsor. All subjects, including those who fail to receive a device according to their randomization but who subsequently receive an alternate commercially available device or procedure will be followed with their initial randomization cohort according to an intent-to-treat analysis. The WaveCrest device may not be used among US subjects randomized to Watchman.

### 6.5 Follow-up Post-Discharge

Follow-up visits will be timed from the Treatment Visit. Following discharge after Treatment Visit, subjects will have office visits at 45 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. Phone follow-up will occur at 3 months, 1.5 years, 2.5 years, 3.5 years and 4.5 years. Table **4** summarizes the schedule of assessments at each protocol-required follow-up visit. All assessments required for each visit must be completed within the visit windows specified in Table 5.

If a subject has experienced stroke symptoms resulting in a QVSFS score > 0 since their most recent follow-up, a board-certified study Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-person neurology visit and exam are unnecessary. An **Unscheduled Neurology Visit** must be completed within 14 days of QVSFS administration or site's awareness of the onset of stroke symptoms (See **Section 6.12** for details of the Unscheduled Neurology Visit).

Subjects who undergo a procedure but are not implanted with an LAA occlusion device must have follow-up per this CIP, with the following exceptions: TEE is not required at follow-up, and antiplatelet and anticoagulant medications should be administered following pre-procedure regimen or administered per physician discretion.

**Note**: Subjects will be followed as Intent-to-Treat. Any subject who does not receive an implant may not be treated with any other LAA device for 45 days.

The following sections describe the requirements for each follow-up office visit and phone follow-up for subjects implanted with an LAA occlusion device.

### 6.6 Follow-up 45 Day Office Visit

- Perform physical exam
- Administer QoL questionnaire (see **Quality of Life Questionnaire - SF-36**)

- Qualified trial personnel who are blinded to subject's randomization and implanted device administer the QVSFS (see **Appendix III: Questionnaire for Verifying Stroke-Free Status**). If the subject has experienced symptoms resulting in a QVSFS score > 0 since their most recent follow-up, a board-certified study Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-person neurology visit and exam are unnecessary. This **Unscheduled Neurology Visit** must be completed within 14 days of the QVSFS administration or site's awareness of the onset of stroke symptoms. (See **Section 6.12** for details of Unscheduled Neurology Visit)
- Perform a TEE following the Echocardiography Protocol and submit images to ECL.
- Cessation of warfarin in the Watchman arm is at physician discretion and should be per the product DFU. If the subject stops warfarin, clopidogrel should be administered per the product DFU.
- Evidence of device thrombus is recommended to be treated with a 6-week course of warfarin (+/- aspirin) and repeat TEE.
- Watchman subjects who discontinue warfarin should be instructed to remain on aspirin daily per the Watchman DFU.
- WaveCrest subjects must remain on dual antiplatelet therapy (DAPT) through 3 months post-procedure.
- Table 3 summarizes the post-procedure anticoagulation and antiplatelet regimen for the duration of trial follow-up.

**Adjunctive Pharmacology Differences and Rationale**

WaveCrest subjects will receive DAPT between the point of implantation and 3 months post-implant (when clopidogrel can be discontinued). This is based on prior experience with the WaveCrest device that suggests a low stroke rate with this regimen. Subjects implanted with the WaveCrest device will be instructed to continue taking 75–100 mg aspirin throughout the study.

Watchman subjects are directed to take warfarin, clopidogrel, and aspirin based on that device's DFU

Aspirin pharmacology studies have demonstrated maximal platelet inhibition with 50 mg of daily aspirin.[53] The risk of gastric erosion increases as aspirin dosage increases. Aspirin 75 -100 mg in the WaveCrest arm has been selected to provide maximal platelet inhibition while minimizing the risk of gastric erosion and aspirin induced gastrointestinal bleeding.

- Record cardiac medications, including antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations as appropriate

### 6.7 3 Months Phone Follow-Up

- For subjects in the WaveCrest arm, if the LAA was closed at 45 days, instruct subject to discontinue clopidogrel but to continue aspirin at the assigned dosage.
- If the LAA was not closed at 45 days, clopidogrel may be continued at Investigator discretion until flow ≤ 5mm is noted in a subsequent TEE.
- Record cardiac medications, including antiplatelet and anticoagulant medications.
- Record adverse events, device malfunctions, and protocol deviations as appropriate.

### 6.8 Follow-up 6 Month Office Visit

- Perform physical exam
- Administer QoL questionnaire (see **Quality of Life Questionnaire - SF-36**)
- Qualified trial personnel who are blinded to subject's randomization and implanted device administer the QVSFS (see **Appendix III: Questionnaire for Verifying Stroke-Free Status**); If the subject has experienced symptoms resulting in a QVSFS score > 0 since their most recent follow-up, a board-certified study Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-person neurology visit and exam are unnecessary. This **Unscheduled Neurology Visit** must be completed within 14 days of the QVSFS administration or site's awareness of the onset of stroke symptoms. (See **Section 6.12** for details of Unscheduled Neurology Visit)
- For subjects in the Watchman arm, if the LAA was closed at 45 days, clopidogrel may be discontinued per the product DFU but aspirin should continue per the product DFU.
- If the LAA was not closed at 45 days and the subject remains on warfarin (Watchman arm) or DAPT (WaveCrest arm), a TEE should be repeated at this visit. Discontinuation of warfarin (Watchman arm) or P2Y12 inhibitor (WaveCrest arm) is at physician discretion but is recommended if peri-device color Doppler flow demonstrated by TEE is ≤ 5mm.
- If an adequate seal is not demonstrated, warfarin (Watchman arm) or P2Y12 inhibitor (WaveCrest arm) may be continued at Investigator discretion until flow ≤ 5mm is noted. Watchman subjects who continue warfarin for 6 months post-implant are not required to start clopidogrel but should remain on aspirin per the product DFU.
- Sites that routinely perform a 6-month TEE as their standard of care (SOC) may perform a TEE in all subjects at that site. This is not required for sites that do not perform a 6-month TEE as part of their SOC.
- Evidence of device thrombus is recommended to be treated with a 6-week course of warfarin (+/- aspirin) and repeat TEE.
- Record cardiac medications, including antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations as appropriate

### 6.9 Follow-up 1 Year Office Visit

- Perform physical exam
- Administer QoL questionnaire (see **Quality of Life Questionnaire - SF-36**)
- Qualified trial personnel who are blinded to subject's randomization and implanted device administer the QVSFS (see **Appendix III: Questionnaire for Verifying Stroke-Free Status**); If the subject has experienced symptoms resulting in a QVSFS score > 0 since their most recent follow-up, a board-certified study Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-person neurology visit and exam are unnecessary. An **Unscheduled Neurology Visit** must be completed within 14 days of QVSFS administration or site's awareness of the onset of stroke symptoms. (See **Section 6.12** for details of Unscheduled Neurology Visit)
- Perform a TEE following the Echocardiography Protocol and submit images to ECL
- If an adequate LAA seal is observed, instruct subject to remain on aspirin dosage as assigned daily indefinitely. Table 3 summarizes the post-procedure anticoagulation and antiplatelet regimen for the duration of trial follow-up.
- If an adequate seal is not demonstrated, warfarin (Watchman arm) or P2Y12 inhibitor (WaveCrest arm) may be continued at Investigator discretion and/or until flow ≤ 5mm is noted.
- Evidence of device thrombus is recommended to be treated with a 6-week course of warfarin (+/- aspirin) and repeat TEE.
- Record cardiac medications, including antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations as appropriate

### 6.10 Follow-up 2 Year, 3 Year, 4 Year and 5 Year Office Visits

At each of the above office visits:

- Perform physical exam
- Administer QoL questionnaire (see **Quality of Life Questionnaire - SF-36**)
- Qualified trial personnel who are blinded to subject's randomization and implanted device administer the QVSFS (see Appendix III: Questionnaire for Verifying Stroke-Free Status). If the subject has experienced symptoms resulting in a QVSFS score > 0 since their most recent follow-up, a board-certified study Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-person neurology visit and exam are unnecessary. An **Unscheduled Neurology Visit must be completed** within 14 days of QVSFS administration or site's awareness of the onset of stroke symptoms. (See **Section 6.12** for details of Unscheduled Neurology Visit).
- Instruct subject to remain on daily aspirin at assigned dosage indefinitely. Table 3 summarizes the post-procedure anticoagulation and antiplatelet regimen for the duration of trial follow-up.

- If an adequate seal was not demonstrated at the 1-year TEE, warfarin (Watchman arm) or P2Y12 inhibitor (WaveCrest arm) may be continued at Investigator discretion.
- Evidence of device thrombus is recommended to be treated with a 6-week course of warfarin (+/- aspirin) and repeat TEE.
- Record cardiac medications, including antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations as appropriate

### 6.11 Follow-up Phone 1.5 Year, 2.5 Year, 3.5 Year and 4.5 Year

The QVSFS must be administered over the phone by blinded trial personnel (see **Appendix III: Questionnaire for Verifying Stroke-Free Status**

If the subject has experienced symptoms resulting in a QVSFS score > 0 since their most recent follow-up, a Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-person neurology visit and exam are unnecessary. An **Unscheduled Neurology Visit** must be completed within 14 days of QVSFS administration or site's awareness of the onset of stroke symptoms. (See **Section 6.12** for details of Unscheduled Neurology Visit)

- Instruct subject to remain on daily aspirin at the assigned dosage indefinitely. Table 3 summarizes the post-procedure anticoagulation and antiplatelet regimen for the duration of trial follow-up.
- If an adequate seal was not demonstrated at the 1-year TEE, warfarin (Watchman arm) or P2Y12 inhibitor (WaveCrest arm) may be continued at Investigator discretion.
- Record cardiac medications, including antiplatelet and anticoagulant medications
- Record adverse events, device malfunctions and protocol deviations as appropriate
- Query subject for adverse events or hospitalizations since last follow-up and document

### 6.12 Unscheduled Neurology Visit

An **Unscheduled Neurology Visit** may be triggered by any of the following:

- Subject-reported stroke/TIA;
- QVSFS score > 0;
- Subject-reported symptoms; or
- Investigator suspects a stroke during a protocol-required office visit or phone follow-up.

A board-certified study Neurologist blinded to subject's randomization and implanted device, to the extent possible, must evaluate the following:

- The likelihood that a "yes" answer on the QVSFS or related symptoms are stroke related (this evaluation may be done over the phone or by reviewing available medical records related to a recent neurology exam).
- If there is no question of or concern for a stroke/TIA and an **Unscheduled Neurology Visit** is not required, in the opinion of the study Neurologist, rationale why this visit is not required must be documented.
- If there is any question of or concern for stroke, the subject must have an **Unscheduled Neurology Visit** within 14 days of QVSFS administration or any reported stroke/TIA. At **Unscheduled Neurology Visits** the following must be performed:
  - If stroke is suspected, the NIHSS and mRS (see **Appendix IV: Neurologic Assessments**) must be administered
  - Brain imaging must be performed (MRI unless contraindicated, then CT), unless recent brain imaging (e.g., from emergency department visit at another hospital) is available and deemed adequate by the study Neurologist, at his/her discretion.
  - If stroke is confirmed, appropriate neurology-guided investigations must be conducted to determine stroke etiology (see **Appendix I: Acronyms and Definitions** for stroke definition and etiology). The following is recommended:
    - Cervical/neck artery imaging (CTA/MTA/carotid Doppler)
    - Intracranial artery imaging (CTA/MTA/transcranial Doppler)
    - 24-hour cardiac monitoring
    - Brain imaging (MRI unless contraindicated, then CT)
    - A TEE evaluation is recommended.
      - If a TEE is indicated, perform a TEE following the Echocardiography Protocol to ascertain the mechanism of stroke and submit images to ECL
    - Subject must have a mRS re-administered 90 (+/- 15) days after any confirmed stroke
  - Any imaging files must be made available for CEC review
  - Document location of any intracranial bleeding

**Table 3: Adjunctive Antiplatelet and Anticoagulant Medication Regimen†**

| Visit | Warfarin* | | Aspirin | | Clopidogrel /P2Y12 Inhibitor | |
|---|---|---|---|---|---|---|
| *Arm* | *Watchman#* | *WaveCrest* | *Watchman#* | *WaveCrest* | *Watchman#* | *WaveCrest* |
| Discharge | Yes | No | Yes<br>Per Watchman DFU | Yes<br>75-100mg | No<br>(unless subject was on P2Y12 inhibitor prior to randomization) | 75mg<br>12-48 hours post-procedure, then daily[a] |
| 45-Day | Cessation per Watchman DFU (if LAA is closed) | No | Yes<br>Per Watchman DFU | Yes<br>75-100mg | 75mg daily with warfarin discontinuation per DFU | 75mg daily[a] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 Month | No[b] | No | Yes<br>Per Watchman DFU | Yes<br>75-100mg | 75mg daily with warfarin discontinuation per DFU | No |
| 6 Month | No[b] | No | Yes<br>Per Watchman DFU | Yes<br>75-100mg | No | No |
| ≥ 1 Year | No[b] | No | Yes<br>Per Watchman DFU | Yes<br>75-100mg | No | No |

[#] All Watchman adjunctive medication should be administered per the product DFU

[†] For subjects not implanted with a LAA occlusion device, antiplatelet and anticoagulant medications will be per physician discretion.

[*] Alternative vitamin K antagonists (e.g., acenocoumarol or phenprocoumon) may be used according to geographic standard of care.

[a] Prasugrel 5-10 mg QD or ticagrelor 60-90 mg BID may be used in place of clopidogrel in subjects unable to take clopidogrel but may not be used with warfarin. Also, prasugrel is contraindicated in subjects with a history of prior stroke/TIA and both are contraindicated in subjects with a history of hemorrhagic stroke.

[b] If subject has remained on warfarin for non-closure, cessation of warfarin remains per Watchman DFU

**Table 4: Schedule of Assessments[†]**

| Assessment | Screening/ Baseline | Treatment Visit (Implant Procedure) | Discharge | Office Visit | | | | Phone Follow-up 3m, 1.5y, 2.5y, 3.5y, 4.5y |
|---|---|---|---|---|---|---|---|---|
| | | | | 45d | 6m | 1y | 2y, 3y, 4y, 5y | |
| **Medical history** | X | | | | | | | |
| **Physical exam** | X | X | X | X | X | X | X | |
| **Blood work** | X | | | | | | | |
| **$CHADS_2/CHA_2DS_2$-VASc** | X | | | | | | | |
| **HAS-BLED score** | X | | | | | | | |
| **TEE[a]** | X | X | | X | X[h] | X | | |
| **TTE[a]** | | | X | | | | | |
| **QVSFS[b]** | X | | | X | X | X | X | X[i] |
| **QoL** | X | | | X | X | X | X | |
| **Neurology exam** | X[f] | | | | | | | |
| **Brain Imaging (MRI – if contraindicated CT)** | X[c] | X[d] | | | | | | |
| **mRS/NIH Stroke Scale** | X | X[g] | | | | | | |
| **Medication Review** | X | X | X | X | X | X | X | X |
| **AE Monitoring[e]** | | X | | | | | | |

[†] Schedule of assessments for subjects implanted with an LAA occlusion device; subjects not implanted with an LAA occlusion device will not have TEE at follow-up.

[a] Follow the **Echocardiography Protocol** from the ECL for all TEE/TTE exams; submit TEE/TTE images from baseline; implant; discharge; 45-day visit; 6-month visit (if applicable);1-year visit, as well as any unscheduled TEEs/TEEs due to AEs to ECL.

[b] Trial personnel must administer the QVSFS. If subject has symptoms resulting in QVSFS score > 0 since their most recent follow-up, a board-certified study Neurologist blinded to subject's randomization assignment and implanted device, to the extent possible, must evaluate the subject or otherwise provide rationale for why an in-

person neurology visit and exam are unnecessary. If there is any concern for stroke, subject must be brought in for **Unscheduled Neurology Visit** within 14 days following QVSFS administration; if stroke is suspected, stroke scale must be administered, and brain imaging must be performed. If stroke is confirmed, and a TEE is performed, to ascertain the mechanism of stroke, follow the **Echocardiography Protocol**. Re-administer mRS 90 days (+/-15) days after stroke.

[c] Brain imaging to be performed at baseline if subject has history of stroke or TIA; if an imaging study following the prior neurologic event is available, repeat imaging is not required per Neurology's discretion

[d] Brain imaging to be performed if stroke or TIA is suspected at any time during follow-up.

[e] Adverse event monitoring is initiated upon the subject signing the informed consent form.

[f] If subject had symptoms resulting in QVSFS score > 0 since their most recent follow-up at any visit or if stroke or TIA is suspected at any time during follow-up, a visit with a board-certified study Neurologist is required. The study Neurologist may waive this visit if it is based solely on QVSFS change with documented rationale.

[g] If stroke is suspected by the study Neurologist, administer NIHSS. Also administer mRS at the visit and 90 (+/-15) days after any confirmed stroke

[h] Per physician discretion if closure is not confirmed with 45-day TEE or if part of study site SOC.

[i] Not required for the 3-month assessment

**Table 5: Visit Windows (from date of Treatment Visit)**

| Follow-up | Type of Follow-up | Window Start Day | Target | Window End Day |
|---|---|---|---|---|
| 45-Day (-5/+15 days) | Office | 40 | 45 | 60 |
| 3-Month (-15/+30 days) | Phone | 76 | 91 | 121 |
| 6-Month (-60/+30 days) | Office | 122 | 182 | 212 |
| 1-Year (-30/+30 days) | Office | 335 | 365 | 395 |
| 1.5-Year (-30/+60 days) | Phone | 517 | 547 | 607 |
| 2-Year (-30/+60 days) | Office | 700 | 730 | 790 |
| 2.5-Year (-60/+60 days) | Phone | 853 | 913 | 973 |
| 3-Year (-60/+60 days) | Office | 1035 | 1095 | 1155 |
| 3.5-Year (-60/+60 days) | Phone | 1218 | 1278 | 1338 |
| 4-Year (-60/+60 days) | Office | 1400 | 1460 | 1520 |
| 4.5-Year (-60/+60 days) | Phone | 1583 | 1643 | 1703 |
| 5-Year (-60/+60 days) | Office | 1765 | 1825 | 1885 |

## 6.13 Subject Trial Completion

Subjects will be considered to have completed participation in the trial when they have completed 5-year follow-up or have discontinued from the trial. The appropriate **eCRF** must be completed for the subject when:

- Subject has completed 5-year follow-up, or
- Subject has died before 5-year follow-up is complete, or
- Subject has requested to withdraw from the trial prior to 5-year follow-up with no further contact or review of charts

When the subject's participation in the clinical trial has been completed the subject will return to the medical care as per physician's recommendation.

### 6.14 Any Known or Foreseeable Factors that May Compromise the Outcome of the Clinical trial or the Interpretation of the Results

All foreseeable factors that may compromise the outcome have been taken into account by clinical trial design and well-defined subject selection criteria.

### 6.15 Criteria and Procedures for Subject Withdrawal or Discontinuation

Every roll-in and randomized subject (including those who did not undergo a Treatment Visit or did not receive a device implant), shall remain in the trial until completion of 5-year follow-up; however, subject participation in any clinical trial 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:

- Subject refuses to continue participation in the trial
- Subject is deceased (cause must be documented)
- Lost-to follow-up (defined below).

It is the Sponsor's intent to apply the principles from FDA's guidance on Data Retention When Subjects Withdraw From FDA-Regulated Clinical Trials to the WAVECREST 2 trial so as to minimize bias and ensure trial integrity. If a subject voluntarily withdraws from the trial, every effort must be made to obtain full information on any new or ongoing adverse events through the date of subject discontinuation.

Investigators must report subject withdrawals to their respective IRB/EC as defined by their institution's procedure. If a subject withdrawal is related to the investigational device, the Investigator shall document the reason for subject discontinuation as related to investigational device and request subject's permission to follow his/her status outside the clinical investigation.

Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) but will not be replaced. At Sponsor's request, the Investigator may consult public records, such as those establishing survival status, after subject withdrawal. Alternatively, the Sponsor may contract with a subject search organization for the Investigator in order to establish survival status of discontinued subjects.

### 6.16 Lost-to-Follow-up (LTFU)

If a subject misses two consecutive scheduled follow-up visits, trial personnel will make all possible attempts to contact the subject per the site's standard of practice. If the Investigator concurs and at least two unsuccessful documented attempts on two different days have been made to contact the subject, the subject will be considered lost-to-follow-up. The date, time and name of site personnel attempting to contact the subject, along with the Investigator's concurring opinion must be documented in the subject's medical records. Upon determination that the subject is LTFU, a letter must be sent to the subject's residence and a copy of the letter saved in the subject's medical records. If a subject who has been considered LTFU is relocated and is interested in remaining in the trial, LTFU status may be revoked with documentation in the subject's medical record along with the associated protocol deviation for missed visits. If a

subject relocates or moves and an Investigator is located in the general area, trial records may be transferred to another site and follow-up continued.

### 6.17 Early Trial termination

The Sponsor reserves the right to terminate the clinical trial at any stage with suitable written notice to the Investigators. Possible reasons for termination are:

- Physician Advisory Committee makes a recommendation for early termination based upon input from the Data Monitoring Committee
- Unanticipated Adverse Device Effects (UADEs) present an unreasonable risk to subjects

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification to the IRB/EC or will notify the EC directly as appropriate for OUS sites. The Sponsor will also notify FDA and Competent Authorities (CAs), as applicable, of trial termination. Should the trial 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.

Should early termination occur, the Investigator shall return all clinical trial materials (including investigational devices) to the Sponsor.

## 7. COMPLIANCE TO CIP

### 7.1 Statement of Compliance

This trial will be conducted in accordance/compliance with this CIP, the most current version of the World Medical Association (WMA) Declaration of Helsinki, ISO14155, and any regional and/or national regulations, as appropriate.

The sites will not start enrolling subjects or request informed consent from any subject prior to obtaining IRB/EC approval and Competent Authority approval, if applicable, execution of appropriate Investigator and/or site agreements, and authorization from the Sponsor in writing for the trial.

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

As Sponsor, Coherex Medical has taken up general liability insurance in accordance with the requirements of the applicable local laws. Appropriate country representatives will be utilized to understand the requirements for the type of insurance that will be provided for subjects, such information will be incorporated into the informed consent, as applicable.

If required, additional subject coverage or a trial specific insurance will be provided by the Sponsor as well.

## 7.2 Adherence to the Clinical Investigation Plan

A deviation is defined as an event where the clinical Investigator, site personnel, Sponsor or Sponsor representative did not conduct the clinical trial according to the CIP, IRB/EC requirements or the Clinical Trial Agreement. The Investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial, and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the Investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the Investigator to provide adequate medical care to a subject enrolled in a trial.

Investigators will inform their IRB/EC of protocol deviations in accordance with their specific IRB/EC reporting policies and procedures.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the CIP. Relevant information for each deviation will be documented.

Regulations require Investigators obtain approval from Coherex Medical and the IRB/EC [as required] before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the IRB/EC. Such deviations shall be documented and reported to the Sponsor and the IRB/EC as soon as possible, but no later than 5 working days.

Prior approval must be requested when the Investigator anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the Investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the Investigator's control, must be reported on a CRF.

All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

In the event an Investigator is not compliant with this CIP, 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 one or more of the following actions

- Visiting the Investigator
- Contacting the Investigator by telephone
- Contacting the Investigator in writing
- Retraining of the Investigator

Repeated non-compliance despite these steps may result in further escalation in accordance with the Sponsor's procedures, including termination of the Investigator's participation in the trial.

## 8. ADVERSE EVENT, ADVERSE DEVICE EFFECTS, DEVICE DEFICIENCY

### 8.1 Definitions

#### 8.1.1 Medical Device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
  - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - Supporting or sustaining life,
  - Control of conception,
  - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

#### 8.1.2 Adverse Event

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 investigational device or comparator. This definition includes events related to the procedures involved.

**Note**: Unchanged, chronic, non-worsening or pre-existing conditions are not adverse events, but any planned treatment or intervention/elective procedure must be reported on the Non-AE/Planned Procedure eCRF.

The Investigator must monitor and report the occurrence of adverse events for each subject from the time of enrollment through all trial follow-up. 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 **eCRF** within 2 weeks from when the investigator becomes aware of the event. 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 must be recorded in standard medical terminology rather than the subject's words. The **eCRF** must be updated as additional information on the event is received. In addition to reporting requirements specified in this CIP, sites must follow the Watchman manufacturer's adverse event reporting requirements for subjects randomized to the Watchman device.

**Relatedness to Device or Procedure**

Relationship of an adverse event to the investigational device (or comparator) or the 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 or procedure relationship of each adverse event will be categorized as the following: not related, unlikely, possible, probable, or causal relationship, as adapted from MEDDEV 2.7/3:

1) Not related: relationship to the device or procedures 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 investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious 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 investigational 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 serious event.

2) 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.

3) Possible: the relationship with the use of the investigational 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 where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

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

5) Causal relationship: the serious event is associated with the investigational 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 investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
    - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
    - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
    - 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 investigator will distinguish between adverse events related to the investigational device and those related to the implant procedure. An adverse event can be related both to the implant procedure and the investigational device.

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”.

### 8.1.3 Serious Adverse Event

An adverse event that led to:

- Death,
- A serious deterioration in health of the subject, that either resulted in:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function, or
    - An inpatient hospitalization or prolongation of existing hospitalization, or

- A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Fetal distress, fetal death or a congenital abnormality or birth defect

**Note**: A planned hospitalization or treatment/elective procedure 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), but must be reported on the Non-AE/Planned Procedure eCRF.

SAEs must be reported to the Sponsor as soon as possible but no longer than 72 hours (or within the timeline specified by site's local IRB/EC requirements, if these requirements are more stringent) on the appropriate **eCRF** from the time trial personnel became aware of the event or became aware that the event met the definition of a serious adverse event. In the event that the eCRF database is not available, the Investigator must report the SAE to the Sponsor via email. The SAE must then be entered as soon as possible in the eCRF. The Investigator must report the SAE to the local IRB/EC according to the IRB/EC reporting requirements.

### 8.1.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device. ADEs must be reported on the appropriate eCRF (AE eCRF) within 2 weeks from when the Investigator becomes aware of the event.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional misuse.

### 8.1.5 Unanticipated Serious Adverse Device Effect (USADE)

A 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. A USADE must be reported as soon as possible but no longer than 72 hours after becoming aware of the event, on the eCRF.

### 8.1.6 Unanticipated Adverse Device Effect (UADE)

As defined in 21 CFR §812.3, unanticipated adverse device effects (UADE) are defined as 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 CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse device effect occurs, the Investigator must notify Coherex Medical as soon as possible but no longer than 72 hours of the Investigator becoming aware of the event on the eCRF. The Sponsor will notify all IRBs/ECs and all Investigators within 10 working days of the Sponsor's knowledge of the event, as required by 21 CFR §812.150. Coherex Medical will

take any steps necessary to investigate the event and will be responsible for notifying FDA and all other participating IRBs/ECs, CAs, as appropriate, and Investigators.

### 8.1.7 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. Such events must be reported on the eCRF no longer than within 72 hours of awareness of the event.

## 8.2 Procedure for assessing, recording and reporting adverse events, device deficiencies/complaints, adverse device effects, serious adverse events and serious adverse device effects:

Safety surveillance within this trial and the safety reporting both performed by the Investigator, starts as soon as the subject is enrolled in this trial (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject/Investigator concludes his/her participation in the trial, or the subject/Investigator withdraws the subject from the trial, except as otherwise specified in the CIP.

All adverse event data including deaths and device deficiency data (if applicable) will be collected throughout the clinical trial and will be reported to the Sponsor through the EDC system.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

Reportable events to the Sponsor are considered:

- All Adverse Device Effects
- All Serious Adverse Events (whether or not the event is considered device- or procedure-related and regardless the randomization group)
- (if applicable) device deficiencies, that could have led to a serious adverse device effect
  - if either suitable action had not been taken;
  - if intervention had not been made or
  - if circumstances had been less fortunate

All above events will be reported to the Sponsor, as soon as possible, but no later than 72 hours of first learning of the event.

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

Additional information may be requested, when required, by the Sponsor or CEC in order to support the reporting of AEs to regulatory authorities.

The Investigator must notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

### 8.3 Subject Death

Subject deaths must be reported as soon as possible but no later than 24 hours (or within the timeline specified by site's local IRB/EC requirements, if these requirements are more stringent) on the appropriate **eCRF** from the day trial personnel become aware of the event. Upon subject death, a trial completion **eCRF** must also be completed. Deaths will be reported as cardiovascular or non-cardiovascular (**Appendix I: Acronyms and Definitions**). In the event that the eCRF database is not available the Investigator must report the SAE to the Sponsor in a timely fashion via email. The death must then be entered as soon as possible in the eCRF once the eCRF database becomes available. The Investigator must report the death to the local IRB/EC according to the IRB/EC reporting requirements. In the event of subject death within 45 days of the implant procedure, an autopsy should be ordered, and the autopsy report submitted to the Sponsor.

### 8.4 Device Deficiency

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

**Note**: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device deficiencies for both arms of the study must be reported to the Sponsor within 3 working days (or within the timeline specified by site's local IRB/EC requirements, if these requirements are more stringent) on the **Device Deficiency eCRF** from the day trial personnel become aware of the event. In the event that the eCRF database is not available the Investigator must report the device deficiency to the Sponsor in a timely fashion via email. The device deficiency must then be entered in the eCRF as soon as possible once the eCRF database becomes available.

Investigational WaveCrest devices opened at the site that meet any of the above criteria should be returned to the Sponsor. An approved biohazardous materials container will be supplied by the Sponsor to return contaminated product, along with instructions to complete this process.

Upon learning of a WaveCrest device deficiency, an investigation will be initiated by the Sponsor to track the handling of the device and report the results of any internal investigations related to the cause of the complaint. Investigation of Watchman device deficiencies should be coordinated with the Watchman manufacturer.

Due to the passive nature of this device, explants are unlikely once the device is implanted. If a WaveCrest device is explanted for any reason, it should be returned to the Sponsor following the steps for returning investigational devices. Explants related to the Watchman device should be coordinated with the Watchman manufacturer.

## 9. DATA MANAGEMENT

Overall, the Sponsor will be responsible for the data handling.

The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

The Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB/EC/Head of Medical Institution review and regulatory authority inspections. As required, the Investigator or institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

## 9.1 Data Management Plan

A detailed **Data Management Plan** (DMP) will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the trial duration. All revisions will be tracked, and document controlled.

Sponsor or designee will regularly perform data review and database cleaning, including issuing queries in accordance with the DMP.

CRF data will be captured in a validated electronic database management system.

Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system utilized by Coherex Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

## 9.2 Document and Data Control

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 trial shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical trial.

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 his/her information shall be preserved in reports and when publishing any data

### 9.2.1 Traceability of documents and data

The Investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by trial personnel with a statement that it is a true reproduction of the original source document. Data reported on eCRFs shall be derived from source documents and be consistent with these source documents. Any discrepancies shall be explained in writing.

### 9.2.2 Recording data

Source documents will be created and maintained by the investigational site team throughout the clinical trial.

The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

### 9.2.3 Records

The Investigator and Sponsor are responsible for maintaining the following accurate, complete, and current records relating to the investigation (See Table 6):

[redacted]

| RECORDS | MAINTAINED BY INVESTIGATOR | MAINTAINED BY SPONSOR |
|---|---|---|
| Any other FDA required records | X | X |

### 9.3 Record Retention

Coherex Medical and the Investigators shall maintain the clinical investigation documents as required by the Sponsor and applicable regulatory requirements. They shall take measures to prevent accidental or premature destruction of these documents.

The Sponsor will archive and retain all documents pertaining to the trial per Sponsor's record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical trial records.

#### 9.3.1 Record Custody

Record custody may be transferred to any other person who will accept responsibility. The FDA will be notified of this transfer no later than ten (10) days after the transfer occurs (812.140 (e)).

#### 9.3.2 Reports

Investigators and Sponsors are responsible for preparing and submitting the following complete, accurate, and timely reports listed in Table 7:

**Table 7: Trial Reports**

| REPORTS | INVESTIGATOR | SPONSOR |
|---|---|---|
| Unanticipated Adverse Device Effects | To IRB/EC and Coherex Medical | To the FDA, all IRB/ECs/CAs all Investigators within ten (10) working days after receiving notice if the event |
| Withdrawal of IRB/EC Approval | To Coherex Medical within five (5) working days | All IRB/ECs/CAs and all Investigators will be notified within five (5) working days |
| Progress Reports | To IRB/EC and Coherex Medical annually | To FDA and IRB/ECs/CAs annually |
| Deviations from the CIP | IRB/EC notification and acknowledgement (if applicable) | FDA if deviation affects the scientific soundness of the CIP |
| Informed Consent | Use of the device without consent must be reported to Coherex Medical and IRB/EC within five (5) days | To the FDA within five (5) working days of receipt of a device implant without informed consent |

| REPORTS | INVESTIGATOR | SPONSOR |
|---|---|---|
| Final reports | Investigators submit a final report to Coherex Medical and the IRB/EC within three (3) months after termination or completion of a trial or the Investigator's part in a trial | A Final Report will be sent to FDA, all IRB/ECs/CAs and Investigators within six (6) months after completion or termination |
| Other reports that may be requested by Coherex Medical or the IRB/EC | Other reports that may be requested by Coherex Medical or the IRB/EC | Reports that may be requested by IRB/EC/CA or FDA |
| Current Investigator List | | Current Investigator List to FDA every six (6) months following trial initiation |
| Recall and device disposition | | FDA and all IRB/ECs/CAs will be notified within 30 working days of the reasons for any request that an Investigator return, repair, or dispose of any devices |
| Withdrawal of FDA Approval | | All IRB/ECs/CAs and all Investigators will be notified within five (5) working days |
| Other | Investigators provide accurate, complete and current information about any aspect of the investigation upon request of the IRB/EC or FDA | Coherex Medical provides accurate, complete and current information about any aspect of the investigation up request of the IRB/EC/CA or FDA |

### 9.3.3 IRB/EC Records

Each reviewing IRB/EC must maintain the following records (21 CFR 56.115):

- All pertinent correspondence relating to the investigation
- All records of membership and affiliations
- Meeting minutes

## 10. MONITORING

Sponsor or Sponsor representatives will monitor the clinical trial to ensure compliance with the Clinical Investigation Plan, signed Investigator's agreement, any conditions imposed by the IRB/EC, terms of the executed Clinical Trial Agreement (CTA), applicable regulations, and accuracy of trial data under Sponsor monitoring procedures and the clinical trial **Monitoring Plan**.

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 accountability. Monitoring will also verify that trial data submitted on electronic case report forms (eCRFs) are complete and

accurate. Data submitted on eCRFs will be verified against source documents (medical records) utilizing the principles specified in FDA's guidance on risk-based monitoring (Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring) that will be detailed in the **Monitoring Plan**.

Clinical monitors shall be qualified through training and experience, as well as knowledge, in Good Clinical Practices, the CIP, the informed consent process, use of the investigational device and comparator, and relevant regulatory requirements. Clinical monitors shall also be trained on relevant procedures to be implemented for this trial, as well as the **Monitoring Plan**. Training shall be documented in Sponsor files.

After enrollment has begun at the site, a Sponsor or contract monitor(s) trained to Coherex Medical's clinical SOPs will conduct a monitoring visit at a frequency based on factors, such as subject accrual rate and observations from previous monitoring visits. The monitor will schedule a visit with the appropriate site staff.

During the monitoring visit, the monitor will evaluate the trial progress, and ensure continual acceptability of the facility, adherence to the CIP, and maintenance of adequate records (See **Section 9 Data Management**). Trial monitors will have access to all records necessary to ensure integrity of the data and will periodically review progress of the trial with the Investigator. If a significant compliance issue or protocol deviation is noted, Coherex Medical will make recommendations and take appropriate actions to resolve the situation.

Clinical monitors will write reports to document site visit activities. Each report will include the following information:

- Date the visit took place
- Name of the monitor who conducted the visit
- Name and address of the Investigator visited
- Identification of persons contacted by the monitor
- Information reviewed during the visit (e.g., informed consent, source documents, regulatory binder, device accountability)
- Review of items discussed, and Action Items generated and resolved
- Additional Comments

In addition, contact between trial monitors and the clinical sites will be maintained by telephone, facsimile, electronic mail, and site visits per the request of the Investigator or at the discretion of Coherex Medical.

The Investigator will collaborate with the clinical monitor to schedule monitoring visits, provide a suitable environment for monitors to access trial-related documents and be available during monitoring visits. A **Visit Sign-In Log** will be maintained at the site.

## 11. SUBJECT INFORMATION

All trial participants are provided with a [redacted] Card regardless of the randomization assignment.

## 12. IRB/EC INFORMATION

Coherex Medical requests a waiver of the requirements under 21 CFR 812.35(b) for submitting certification of IRB/EC approval to the FDA prior to beginning the investigation at a particular site. In lieu of this requirement Coherex Medical will submit an IRB/EC and Investigator list update in 6-month intervals.

## 13. OTHER INSTITUTIONS

There are no other institutions that are part of this trial other than the investigative sites and designated echo core lab.

## 14. REGULATORY INSPECTIONS

The Investigator and/or delegate must contact Coherex Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the Investigator and/or delegate in preparing for the audit.

An Investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An Investigator, or any person acting on behalf of such a person with respect to the trial, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the trial.

An Investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the Investigator, to the Sponsor or IRB/EC have not been submitted or are incomplete, inaccurate, false or misleading.

### 14.1 Audits

Audits of this clinical investigation may be conducted by the Sponsor or by third parties designated by the Sponsor, to evaluate compliance with this Clinical Investigation Plan, written procedures, and applicable regulatory requirements. Individuals assigned to audit ("auditor") shall be qualified by experience and shall be different from those responsible for or involved directly in the conduct of the trial. At the end of each audit, the auditor shall prepare an audit report and an audit certificate verifying that the audit was conducted and submit them to the Sponsor.

In case of site audits by a regulatory body, the Sponsor must be notified. The Sponsor shall provide support for such audits as needed.

## 15. STATISTICAL METHODS

This section summarizes the statistical methods for the WAVECREST 2 clinical trial. A detailed statistical analysis plan describing the sample size calculations and detailed statistical methods that will be applied to the data collected in this trial will be contained in a separate document entitled **Statistical Analysis Plan** which supersedes this summary. This document will be finalized prior to un-blinding of the database and any analysis of the data

### 15.1 Analysis Plan

Statistical analyses will be carried out on the following trial populations.

- **Intention-to-Treat (ITT):** This cohort consists of all randomized subjects regardless of treatment received.
- **Modified Intention-to-Treat (mITT):** This cohort consists of randomized subjects who have vascular access attempted for the implant procedure of the intended LAA occlusion device.
- **Per-Protocol:** This cohort consists of all randomized subjects who receive treatment as randomized and have no major protocol deviations.

### 15.2 Trial Endpoints

The trial is designed to demonstrate non-inferiority for both the safety and the effectiveness endpoints.

The primary safety endpoint is a composite of all death, procedure- or device-related complications requiring percutaneous or surgical intervention through 45 days post-procedure or major bleeding throughout the duration of the trial.

The primary effectiveness endpoint is a composite of ischemic stroke or systemic embolism at 24 months.

[redacted]

[redacted]

## 15.3 Primary Safety Endpoint

The primary safety endpoint for WAVECREST 2 is a composite of all death, procedure- or device-related complications requiring percutaneous or surgical intervention through 45 days post-procedure or major bleeding throughout the duration of the trial.

Let $q_{WAVECREST}$ be the primary safety endpoint rate at 24 months in the device arm, while $q_{CONTROL}$ is the corresponding rate in the control arm. Specifically, the following null and alternative hypotheses will be tested:

$$H_0: q_{WAVECREST}/q_{CONTROL} \geq 1.75 \text{ vs.}$$
$$H_a: q_{WAVECREST}/q_{CONTROL} < 1.75$$

The primary safety endpoint rate will be calculated in each treatment arm using a piecewise [redacted]

## 15.4 Primary Effectiveness Endpoint

The primary effectiveness endpoint for WAVECREST 2 is the 24-month rate of ischemic stroke or systemic embolism. [redacted]

[redacted]

Let $p_{WAVECREST}$ be the primary effectiveness endpoint rate at 24 months in the device arm, while $p_{CONTROL}$ is the corresponding rate in the control arm. Specifically, the following null and alternative hypotheses will be tested:

$$H_0: p_{WAVECREST} / p_{CONTROL} \geq 1.75$$
$$H_a: p_{WAVECREST} / p_{CONTROL} < 1.75$$

[redacted]

## 15.5 Secondary Effectiveness Endpoints

The first secondary effectiveness objective is to establish non-inferiority of the rate of LAA closure at 45 days for the WaveCrest arm compared to the control arm. The rate will be calculated as the number of subjects who have residual flow ≤ 5 mm based on the 45-day TEE divided by the number of subjects in each group with a 45-day TEE. Let $r_{WAVECREST}$ be the 45-day LAA closure rate in the device arm, while $r_{CONTROL}$ is the corresponding rate in the control arm. Specifically, the following null and alternative hypotheses will be tested:

$$H_0: r_{WAVECREST} - r_{CONTROL} \geq 8.0\% \text{ vs.}$$
$$H_a: r_{WAVECREST} - r_{CONTROL} < 8.0\%.$$

The other secondary effectiveness objective is to demonstrate reduction in risk of ischemic stroke or systemic embolism with the WaveCrest device in comparison to the $CHADS_2$ and $CHA_2DS_2$-VASc imputed risk of ischemic stroke or systemic thromboembolism in the absence of anticoagulant therapy.

The rate of ischemic stroke in subjects receiving the WaveCrest device in the Treatment Arm will be tested against a performance goal. The hypotheses to be tested are as follows:

$$H_0: \text{lw} \geq 6.0$$
$$H_1: \text{lw} < 6.0$$

[redacted]

### 15.6 Descriptive Endpoints

A number of descriptive safety, effectiveness, and procedural endpoints are included in this trial, and will be summarized by randomized arm (WaveCrest or Watchman).

**Descriptive Safety Endpoints**

The following safety endpoints will be descriptively summarized:

- Components of the primary safety composite endpoint through 45 days post-procedure
- The rates of stroke (all types) or pericardial effusion through 45 days post-procedure
- Pericardial effusion requiring surgical drainage through 7 days post-procedure or at hospital discharge, whichever is later
- Device- or procedure-related Serious Adverse Events (SAEs) reported by site at 45 days, 6 months, and at each annual follow-up period
- All-cause mortality at the time of primary analysis, at each annual follow-up period after the primary analysis, and at the end of trial follow-up (5 years)
- Cardiovascular mortality at the time of primary analysis, at each annual follow-up period after the primary analysis, and at the end of trial follow-up (5 years) - see definition in **Appendix I: Acronyms and Definitions**

**Descriptive Effectiveness Endpoints**

The following effectiveness endpoints will be descriptively summarized:

- Primary effectiveness event rate at 6 months, 3 years, 4 years and 5 years
- Composite of all stroke, systemic thromboembolism, or TIA at 45 days, 6 months, and at each annual follow-up period
- Landmark analysis of primary effectiveness endpoint from the 45-day visit to the time of each annual follow-up period
- Landmark analysis of the incidence of ischemic stroke from 6 months following device implantation and discontinuation of oral anticoagulant and dual antiplatelet therapy
- Composite of all-cause stroke at 45 days, 6 months, and at each annual follow-up period
- Incidence of thrombus on the surface of the device at 45 days, 1 year, and throughout all follow-up
- Strokes adjudicated as ischemic, hemorrhagic, or indeterminate at 45 days, 6 months, and at each annual follow-up period - see definition in **Appendix I: Acronyms and Definitions**
- Strokes adjudicated as major or minor at 45 days, 6 months, and at each annual follow-up period - see definition in **Appendix I: Acronyms and Definitions**
- Stroke adjudicated as cardioembolic in origin at 45 days, 6 months, and at each annual follow-up period - see definition in **Appendix I: Acronyms and Definitions**
- Freedom from oral anticoagulants after each protocol-required follow-up visit
- Number of devices used per subject
- Procedural success – see definition in **Appendix I: Acronyms and Definitions**
- Technical success – see definition in **Appendix I: Acronyms and Definitions**
- Device success – see definition in **Appendix I: Acronyms and Definitions**
- LAA closure rate at 45 days, 6 months, and 1 year as reported by the ECL– see definition in **Appendix I: Acronyms and Definitions**
- Procedure time, device duration, contrast usage, and fluoroscopy time

[redacted]

[redacted]

[redacted]

## 15.8 Trial Success

The trial will be considered successful if both the primary effectiveness and primary safety endpoints are met.

[redacted]

[redacted]

[redacted]

## 16. DOCUMENT RETENTION

The Investigator will maintain all clinical trial documents from prior to, during and (as specified) after the clinical trial on file at the site for a minimum of 2 years after the termination of this trial, or when it is no longer needed to support a marketing application, whichever is later, or longer as per local laws.

The Investigator must contact the Sponsor prior to destroying or archiving off-site any records and reports pertaining to this trial 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 site, the Investigator will notify the Sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit.

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

Coherex Medical and the Investigators will maintain the clinical trial documents as required by Coherex Medical, Inc. and applicable regulatory requirements. They will take measures to prevent accidental or premature destruction of these documents. The Investigator or Coherex Medical may transfer custody of records to another person/party and document the transfer at the investigational site or at Coherex Medical's facility.

**U.S. Requirements**

Clinical trial documents must be retained by the investigational site for a period of 2 years after the latter of the following dates (812.140(d)):

- The date on which the investigation is terminated or completed
- the date the records are no longer required for purposes of supporting an application to the FDA to market the device

All documents must be made available for monitoring or auditing by Coherex Medical's representative or representatives of the FDA and other applicable regulatory agencies. The Investigator must ensure the availability of source documents from which the information on the case report forms was derived.

## 17. AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Trial related documents such as, the Investigator Brochure (IB), Report of Prior Investigations (RPI) CIP, CRFs, Informed Consent form and other subject information, or other clinical trial

documents will be amended as needed throughout the clinical trial, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the Sponsor and the Co-Principal Investigators.

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB/EC and regulatory authorities, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the Investigator at the subject's next follow-up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the Investigators. This information will be incorporated when an amendment occurs.

## 18. TRIAL COMMITTEES

### 18.1 Physician Advisory Committee

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. [redacted] he committee will meet as needed to review trial progress and may advise the Sponsor on potential trial modifications during the trial conduct phase. The committee will advise the Sponsor on actions to be taken upon recommendations from the Data Monitoring Committee (DMC). The Physician Advisory Committee will also make recommendations regarding any publications arising from data generated from the trial.

### 18.2 Clinical Event Committee (CEC)

A Clinical Events Committee (CEC) composed of physicians from different specialties will be appointed by the Sponsor to adjudicate primary effectiveness and safety endpoints, secondary endpoints, death (cardiovascular vs. non-cardiovascular), and bleeding categories. CEC members will not be on the Physician Advisory Committee or Investigators in the trial. The CEC will be composed of at least 4 physicians: 2 stroke Neurologists and 2 Cardiologists. Each CEC meeting will require a quorum. The names of the CEC members, responsibilities of the CEC, the frequency of CEC meetings, the adjudication process and the process for documentation of the adjudication outcome will be specified in a **CEC Charter**. CEC members will be blinded to subject's randomization assignment and implanted device.

### 18.3 Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be appointed by the Sponsor to review on a regular basis accumulating data from the trial. The DMC will advise the Sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial and evaluate results from interim analyses to

provide recommendations to the Sponsor on stopping enrollment and declaring early success. Based on accumulating data from the trial, the DMC will recommend whether to continue, suspend, modify or stop the trial. The DMC will be composed of at a minimum one statistician and 2 physicians. The composition, responsibilities, frequency of DMC meetings, handling of emergency situations and documentation of DMC meetings will be specified in a **DMC Charter**.

## 19. OUTSOURCING OF DUTIES AND FUNCTIONS

The Sponsor may transfer any or all of the duties and functions related to the clinical trial, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical trial will reside with the Sponsor. All requirements applying to the Sponsor will also apply to the external organization inasmuch as this organization assumes the clinical trial related duties and functions of the Sponsor.

### 19.1 Echocardiography Core Lab

An Echocardiography Core Laboratory (ECL) will be appointed by the Sponsor to assess TEEs for LAA closure and presence of device thrombus and TTEs for pericardial effusion post-procedure. The ECL will also assess post-stroke TEEs to ascertain the mechanism of stroke. The ECL will provide an ***Echocardiography Protocol*** and training to investigational sites. The responsibilities and processes to be followed by the ECL will be described in an ***ECL Manual of Operations.***

## 20. INVESTIGATION SUSPENSION OR TERMINATION

### 20.1 Premature trial termination

The Sponsor reserves the right to stop the trial at any stage, with appropriate written notice to the Investigator.

Possible reasons for early termination of the trial by the Sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision
- Recommendation from DMC to Physician Advisory Committee and Sponsor
- Request from Regulatory bodies
- Request of Ethics Committee(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse device effects within 10 working days to Sponsor and the EC, as required
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008

- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

The trial will be terminated according to applicable regulations.

The Investigator may also discontinue participation in the clinical trial with appropriate written notice to the Sponsor.

Should either of these events occur, the Investigator will return all documents to the Sponsor; provide a written statement as to why the premature termination has taken place and notify the IRB/EC and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

An Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical trial at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical trial or when so instructed by the IRB/EC or regulatory authority, Coherex Medical may suspend the clinical trial as appropriate while the risk is assessed. Coherex Medical will terminate the clinical trial if an unacceptable risk is confirmed.

Coherex Medical will consider terminating or suspending the participation of a particular investigational site or Investigator in the clinical trial if monitoring or auditing identifies serious or repeated deviations on the part of an Investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Investigator and Coherex Medical will keep each other informed of any communication received from IRB/EC or regulatory authority.

If for any reason Coherex Medical suspends or prematurely terminates the trial at an individual investigational site, Coherex Medical will inform the responsible regulatory authority, as appropriate, and ensure that the IRB/EC are notified, either by the Investigator or by Coherex Medical. If the suspension or premature termination was in the interest of safety, Coherex Medical will inform all other Investigators.

If suspension or premature termination occurs, Coherex Medical will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical trial, and the Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

### 20.2 Resuming the trial after temporary suspension

When Coherex Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, Coherex Medical will inform the Investigators, IRB/EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision.

Concurrence will be obtained before the clinical trial resumes from the IRB/EC or regulatory authority where appropriate.

If subjects have been informed of the suspension, the Investigator or authorized designee will inform them of the reasons for resumption.

### 20.3 Trial conclusion

The trial will be concluded when:

- All sites are closed AND
- The Final Report generated by Coherex Medical or Coherex Medical has provided formal documentation of trial closure

## 21. TRAINING

### 21.1 Training of Investigators and Trial Personnel

Investigators and trial personnel who will be responsible for day-to-day activities for the trial must have completed GCP training per the sites standard operating procedures. Sponsor will provide training on the WAVECREST 2 CIP and the eCRF database.

Additionally, Sponsor will provide training on WaveCrest device IFU to implanting physicians and imaging training for the implant procedure to echocardiographers assigned to the trial. 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.

Certification of implanting Investigators will be based on a competency assessment. On-site case support will be provided by the Sponsor for all implant procedures. Prior to each procedure, a review of baseline imaging studies may be conducted by one of Sponsor's certified clinical trainer with the Investigator.

The echocardiographer will receive imaging training for the implant procedure from the Sponsor. The Sponsor will provide training to echocardiographers on the **Echocardiography Protocol**.

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

Table 8 describes the training modules required for the specific roles for trial personnel (Investigator, trial coordinator, echocardiographer and blinded trial personnel who will administer the QVSFS) assigned to the trial:

[redacted]

## 22. PUBLICATION POLICY

Results of this clinical trial will be submitted for publication without regard for whether the trial results are positive or negative. The Physician Advisory Committee will be responsible for oversight of the publication process. The Physician Advisory Committee (or a Publication Committee appointed by the Sponsor and Physician Advisory Committee) will have oversight of publications of results of the trial. Site-specific clinical trial results may be published by Investigators in compliance with the Clinical Trial Agreement.

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

This trial will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

Upon receiving IDE approval from the FDA, this clinical trial will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website no later than 12 months after trial completion, as required by Section 801 of the FDA Amendments Act. If this clinical trial is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

# APPENDIX I: Acronyms and Definitions

**ACRONYMS**

| | |
|---|---|
| AF | Atrial Fibrillation |
| CAS | Carotid artery surgery |
| CBC | Complete Blood Cell |
| CEA | Carotid endarterectomy |
| CEC | Clinical Events Committee |
| CT | Computed tomography |
| DMC | Data Monitoring Committee |
| EC | Ethics Committee |
| ECL | Echocardiography Core Lab |
| eCRF | Electronic Case Report Form |
| ePTFE | Expanded polytetrafluoroethylene |
| GI | Gastrointestinal |
| HGB | Hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act |
| IDE | Investigational Device Exemption |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LAA | Left Atrial Appendage |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| NIH | National Institutes of Health |
| OAC | Oral Anticoagulant – synonymous with “anticoagulant” |
| NYHA | New York Heart Association |
| QVSFS | Questionnaire for Verifying Stroke-Free Status |
| TEE | Transesophageal Echocardiogram |
| TIA | Transient Ischemic Attack |
| TTE | Transthoracic Echocardiogram |
| WBC | White Blood Cell |

## DEFINITIONS

| | |
|---|---|
| **Anticoagulant** | Medication used to reduce thrombogenic properties of blood regardless of mechanism or action (Abbreviated OAC) |
| **Antiplatelet** | Medication used to inhibit platelet aggregation (P2Y12 inhibitor; aspirin) |
| **Atrial Fibrillation** | |
| Paroxysmal | • AF that terminates spontaneously or with intervention within 7 days of onset.<br>• Episodes may recur with variable frequency. |
| Persistent | • Continuous AF that is sustained > 7 days and < 12 months |
| Long-Standing Persistent | • Continuous AF that is sustained > 12 months |
| Permanent | • Continuous AF that is sustained > 12 months that cannot or is not planned to be resolved with treatment<br>• 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. |
| **Cardiac Tamponade** | Compression of the heart by an accumulation of fluid or air in the pericardial sac (i.e., Pericardial Effusion). Cardiac tamponade may range from asymptomatic to life-threatening in severity and may include one or more of the following characteristics:<br>• Hypotension, jugular venous distension, and/or muffled heart sounds<br>• Chest pain, palpitations, shortness of breath, or in more severe cases, dizziness, syncope and altered mental status<br>• Pulseless electrical activity cardiac arrest<br>• Pulses paradoxus (decrease in systolic blood pressure >10 mm Hg with inspiration)<br>• Sinus tachycardia, low voltage, or electrical alternans on ECG<br>• Enlarged cardiac silhouette on chest X-ray<br>• Echocardiographic findings including pericardial effusion, right ventricular diastolic collapse, right atrial systolic collapse, hepatic veins indicating elevated systemic venous pressure, reduced left ventricular end-diastolic and end-systolic dimensions, reduced stroke volume & cardiac output, inspiratory bulge/bounce of the interventricular septum into the left ventricle, abnormal respiratory changes in Doppler flow velocity, and plethoric IVC<br>• Requiring interventional or surgical drainage |
| **Clinical Trial/ Clinical Study** | For purposes of this trial and all related documents (i.e., Informed Consent, Clinical Trial Agreement, etc.) the terms trial and study are used interchangeably. |
| **Device Duration** | Time from introduction of delivery sheath to removal of delivery sheath |
| **Left Atrial Duration** | Time from transseptal puncture to removal of delivery sheath |
| **Device Embolization** | A device that has migrated from the Left Atrial Appendage 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- |

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| **Myocardial Infarction** *3rd Universal Definition (see Thygesen, et al. Circulation. 2012;126:2020-2035 for additional details*) | Acute Myocardial Infarction (AMI) - Evidence of myocardial necrosis consistent with acute myocardial ischemia. Any one of the following meets MI diagnosis:<br>• Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference level (URL) and with at least one of the following:<br>o Symptoms of ischemia<br>o New/presumed new significant ST-segment-T wave (ST-T) changes or new LBBB<br>o Development of pathological Q waves in ECG<br>o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality<br>o Identification of an intracoronary thrombus by angiography or autopsy<br>• Cardiac Death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased<br>• For PCI-related MI or Prior MI – please see Thygesen, et al. |
| **Procedure Duration** | Time from venous puncture to removal of delivery catheter |
| **Technical Success** | • Occlusion of the LAA<br>• No device-related complications<br>• No leak >5mm on color Doppler TEE |
| **Procedural Success** | • Technical success<br>• 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) |
| **Device Success** | • Device deployed and implanted in the correct position |
| **Death** | VARC II Definition[54] |
| **Cardiovascular Death** | Death that meets any of the following criteria:<br>• Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure)<br>• Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease<br>• Procedure-related death, including death related to complication of the procedure or treatment for a complication of the procedure<br>• Valve-related death including structural or non-structural valve dysfunction or other valve-related adverse events<br>• Sudden or unwitnessed death<br>• 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** | Fulfillment of the Duke endocarditis criteria[55] (see http://www.medcalc.com/endocarditis.html) |
| **LAA Closure** | No residual leak or if leak is present, residual gap ≤ 5mm (assessed by the ECL) |
| **Major Bleeding** | Bleeding Academic Research Consortium (BARC)[56]definition |
| Type 3a | Overt bleeding plus hemoglobin drop of 3 to < 5g/dL* (provided hemoglobin drop is related to bleed)<br>Any transfusion with overt bleeding |

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|---|---|
| Type 3b | Overt bleeding plus hemoglobin drop ≥ 5g/dL* (provided hemoglobin drop is related to bleed)<br>Cardiac tamponade<br>Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)<br>Bleeding requiring intravenous vasoactive agents |
| Type 3c | Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)<br>Subcategories confirmed by autopsy or imaging or lumbar puncture<br>Intraocular bleed compromising vision |
| Type 4 | CABG-related bleeding - Perioperative intracranial bleeding within 48 h<br>Reoperation after closure of sternotomy for the purpose of controlling bleeding<br>Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†<br>Chest tube output ≥2L within a 24-h period |
| Type 5 | Fatal bleeding |
| **Major Vascular Complication** | Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous 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 |
| **Pericardial Effusion (PE)** | The presence of an abnormal or unexpected amount (>10mm) of fluid or air in the pericardial space identified using echocardiography as echo-free space between the epicardium and parietal pericardium throughout the cardiac cycle. For the purposes of this study, PEs must include one or more of the following:<br>1) Be accompanied by chest pain or other clinical symptoms (see definition of Cardiac Tamponade)<br>2) Have an increase of >10mm from baseline in either the width (circumferential) or largest measured dimension (loculated) by echocardiographic imaging<br>3) Require percutaneous or surgical drainage<br><br>Pericardial effusions can be further characterized as follows:<br>- Onset: Acute (intra-procedural), Subacute (post-procedure – 60 days), Long-term (>60 days)<br>- Size: Mild (≤10mm), Moderate (11-20mm), Large (>20mm)<br>- Distribution: Circumferential or Loculated<br>- Hemodynamics: With or without Cardiac Tamponade or Effusive-Constrictive<br>- Type: Transudate, Exudate, Hydropericardium (transudate, plasma ultrafiltrate), Hemopericardium (blood in pericardial space), Chylopericardium (chylous pericardial fluid), Pyopericardium (purulent pericardial effusion), or Pneumopericardium (air in the pericardium) |
| **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. |
| **Roll-In** | WaveCrest subjects enrolled prior to a site's randomization phase who had vascular access attempted |
| **Stroke/TIA** | |
| All Stroke | Any ischemic, hemorrhagic, or indeterminate 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 not considered a stroke. Ischemic stroke with hemorrhagic transformation is also categorized here. |
| Hemorrhagic Stroke | Any 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 mRS score > 2 points that persists at 90 days post-stroke |
| Minor Stroke | • Stroke symptoms which last longer than 24 hours with evidence of tissue injury but which does not meet definition of Major Stroke |
| Stroke of Cardioembolic Origin | Using ASCOD Classification system[57]<br>Stroke will be considered cardioembolic except if there is:<br>• Another "potentially causal" mechanism is identified (any of A1, S1, O1, D1) |
| **Systemic Thromboembolism** | Any peripheral ischemic event evidenced by ischemic tissue or radiologic imaging evidence of perfusion deficit |
| **Vulnerable Population** | Individuals whose willingness to volunteer in a clinical trial 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<br>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: $CHADS_2$, $CHA_2DS_2$-VASc and HAS-BLED Scores

The $CHADS_2$ score was developed from five clinical parameters to identify non-valvular AF patients at an elevated risk for ischemic stroke. One point is added for patients who have the following: congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus. Two points are given for patients with a prior stroke/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. This limitation is overcome by the use of the $CHA_2DS_2$-VASc score, which is another ischemic stroke risk stratification method in subjects with non-valvular atrial fibrillation[19]. The score assigns 1 or 2 points for each of the following risk factors: congestive heart failure, hypertension (defined as blood pressure consistently above 140/90), age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65 to74 years, female gender. 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 trial must have a minimum $CHA_2DS_2$-VASc score of 3 or a minimum $CHADS_2$ score of 2.

| **$CHADS_2$** | | **$CHA_2DS_2$-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)

The HAS-BLED Score[43] is one of the tools currently available to assess bleeding risk in AF subjects. The score assigns 1 point for the presence of each of the following: hypertension (uncontrolled systolic blood pressure > 160 mmHg), abnormal renal and/or liver function, previous stroke, bleeding tendency or predisposition, labile INRs, elderly and concomitant drugs and/or alcohol excess. The score ranges from 0 to 9, with scores ≥ 3 indicating high risk of bleeding. This score will be calculated for all subjects but will not be used to determine eligibility in the trial.

**Bleeding Risk Stratification with HAS-BLED Score**

| Risk Factor | Points |
|---|---|
| Hypertension (systolic blood pressure > 160mmHg) | 1 |
| Abnormal renal and liver function* (1 point each) | 1 or 2 |
| Stroke | 1 |
| Bleeding tendency/predisposition* | 1 |
| Labile INRs (if on warfarin)* | 1 |
| Elderly (e.g., age > 65 years) | 1 |
| Medication predisposing to bleeding (antiplatelet, NSAID, etc.) | 1 |
| Drugs or alcohol (>8 drinks/week) (1 point each)* | 1 |
| **Maximum Score** | **9** |

[a] Abnormal renal function is classified as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 200 mmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit of normal, etc.), history of bleeding or predisposition (anemia), labile INR (i.e., time in therapeutic range < 60%), concomitant antiplatelets or nonsteroidal anti-inflammatory drugs, or excess alcohol.

## 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, mini-stroke 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).

# APPENDIX IV: Neurologic Assessments

## Modified Rankin Scale

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

## NIH Stroke Scale

Refer to: https://stroke.nih.gov/documents/NIH_Stroke_Scale.pdf

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