AMPLATZER™ Cardiac Plug (ACP)

Clinical Investigational Plan

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Sponsored by:

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ACP Clinical Trial

Investigational Plan Signature Page

I have read and agree to adhere to the investigational plan and all regulatory requirements applicable in conducting this clinical study. I will provide copies of this investigational plan and all pertinent information to study personnel and will discuss this information with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, to other applicable regulations, to applicable laws, and to hospital Institutional Review Board (IRB).

Investigator:

_____

Print or Type Name

_____

Signature

_____

Date

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1. PURPOSE

CESSATION OF ENROLLMENT

Refer to Appendix D for update on enrollment and changes to follow-up schedules for already enrolled patients.

1.1 NAME AND INTENDED USE OF THE DEVICE

The AMPLATZER™ Cardiac Plug (ACP) is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in subjects who have nonvalvular atrial fibrillation.

1.2 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of the ACP in subjects with nonvalvular atrial fibrillation by demonstrating that the device is non-inferior to optimal medical therapy (OMT) with respect to the primary effectiveness endpoint and superior to OMT with respect to primary safety endpoint.

The OMT control will include subjects managed with oral anticoagulation therapy (warfarin or dabigatran) with therapy choice determined by the clinical judgment of the investigator.

1.3 STUDY DESIGN

The ACP will be clinically evaluated through a prospective, randomized, multicenter, active control study to evaluate safety and effectiveness. The randomization scheme will be 2:1, stratified by study center, oral anticoagulant therapy (OAC) (warfarin or dabigatran), and baseline concomitant aspirin usage. Twice as many subjects will be randomized to the treatment arm (device arm) than to the control arm (OMT), respectively. The study will be initiated under a feasibility phase to be followed by an expanded pivotal phase.

Feasibility phase-Following randomization, the first 30 subjects to receive the device will constitute the feasibility subset. The 45 day results (reported AEs and TEE) for these initial 30 subjects who receive the device or who undergo an implant attempt will be reviewed and adjudicated by the DSMB and then reported to the FDA. Subject enrollment will be temporarily halted while the feasibility subset data are being collected and reviewed by the DSMB and FDA.

1.4 STUDY ENDPOINTS

1.4.1 Feasibility Study Endpoint - 45 day Serious Adverse (SAE) Event Rate

The 45 day results (SAE rate and TEE) in the first 30 subjects who receive the device or who undergo an implant attempt will be reported to the FDA. All reported AEs will be adjudicated to determine their severity in subjects in whom device placement is attempted, from the time of the procedure through 45 days post procedure.

1.4.2 Pivotal Study Endpoints

1.4.2.1 Primary Safety Endpoint

The primary safety endpoint will be evaluated through two hypotheses:

1. **Acute safety** -This analysis compares the rate of procedure related serious adverse events as listed below, that occur in the device arm from the time of randomization until hospital discharge to a performance goal (PG) determined from literature reported rates for similar procedural techniques.

   - Procedure-related death (i.e., death occurring during the implantation procedure)
   - Pericardial effusion requiring treatment
   - Device embolization
   - Access site-related bleeding requiring transfusion ≥ 2 units
   - Damage to other cardiac or major non-cardiac cardiovascular structures

2. **Long-term safety** -This analysis compares safety events as listed below, that occur between the device arm and the control arm. For both the device arm and the control arm these events will be evaluated from the time of randomization to 2 years.

   1. All-cause death
   2. Major bleeding defined as:
      - Symptomatic intracerebral or intraventricular hemorrhage; or subdural, subarachnoid, epidural, or ocular hemorrhage; or
      - Major non-cerebral bleed-defined as transfusion requiring ≥2 units, hospitalization requiring any transfusion or surgical or percutaneous interventional procedure to treat bleeding.

        Note: procedure-related pericardial effusions requiring treatment will not be counted as a major non-cerebral bleed.

1.4.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the occurrence of ischemic stroke and peripheral thromboembolism.

Ischemic Stroke is defined as acute focal neurological deficit presumed to be due to focal ischemia, with either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.

Peripheral Thromboembolism is defined as an abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism.

1.4.3 Secondary Endpoints

Secondary Endpoints to be assessed are:

1. In-hospital procedure success - defined as successful implantation of the ACP device with no reported in-hospital serious adverse events in subjects randomized to the treatment arm

2. "Day 45" clinical success - defined as in-hospital procedure success, closure of LAA documented at Day 45 TEE, no ischemic stroke or peripheral thromboembolism, and discontinuation of warfarin or dabigatran

3. Long-term clinical success - defined as in-hospital procedure success, closure of LAA documented at Day 45 TEE, no ischemic stroke or peripheral thromboembolism, and sustained discontinuation of dabigatran or warfarin (without temporary re-administration) at last available follow-up. 'Sustained discontinuation' is defined as the subject's ability to remain off of dabigatran or warfarin for a minimum of 6 months following discontinuation except in subjects with less than 6 months of follow-up (see below).

   'Sustained discontinuation' for those subjects who have less than 6 months of follow-up is defined as the subject's ability to remain off of dabigatran or warfarin for a minimum of 3 months following discontinuation.

4. Device or procedure-related adverse events to include:

   - Device embolization
   - Myocardial perforation (hemopericardium) or any pericardial effusion requiring drainage
   - Endocarditis
   - Thrombus on device

5. Asymptomatic intracerebral or intraventricular hemorrhage

6. Atrial Fibrillation status - specifically defined as those subjects who progress from paroxysmal to persistent AF, or those subjects who progress from persistent to permanent AF

7. Technical success – defined as delivery and release of the ACP device, including recapture and/or replacement, as necessary. This success rate will be calculated among subjects in whom the delivery system enters the body.

8. Transient Ischemic Attack - defined as acute focal neurological deficit (such as focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax,

blindness, or focal visual deficit) presumed due to focal ischemia, with symptoms persisting greater than or equal to 5 minutes and less than 24 hours, and that is not associated with MR or CT findings of a new cerebral infarct.

9. Complete closure – defined as the absence of flow into the LAA at six (6) months as assessed by TEE.

1.5 DURATION OF THE INVESTIGATION AND SAMPLE SIZE (REFER TO APPENDIX D)

The ACP clinical trial will enroll a minimum of 400 and maximum of 3000 subjects at a maximum of 80 investigative sites in the United States and a maximum of 10 sites in Canada. The anticipated study duration is approximately 5 years. Safety and effectiveness data collected from the randomized subjects will be used to support a PMA submission.

2. CLINICAL PROTOCOL

2.1 BACKGROUND INFORMATION

DISEASE TO BE TREATED

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder (Fuster 2006). During AF there are multiple simultaneous waves of contraction which spread in a chaotic manner through both atria. This arrhythmia results in rapid, uncoordinated contractions which decrease the blood pumped through the atria.

Atrial fibrillation is classified as valvular, nonvalvular, or lone. Nonvalvular AF refers to cases without rheumatic mitral valve disease, prosthetic heart valve, or valve repair. Nonvalvular AF can be further classified according to the AHA/ACC/ESC guidelines as paroxysmal, persistent, and/or permanent. Paroxysmal AF has been reported in an estimated 25 to 90% of subjects with AF (Kannel 1983, Davidson 1989, Phillips 1990, Gajewski 1981, and Takahashi 1981) although 90% of cases of paroxysmal AF are asymptomatic and therefore the prevalence may not be known (Israel 2004, Page 1994). Paroxysmal AF terminates spontaneously whereas persistent AF is sustained for a minimum of seven days. Persistent or paroxysmal AF, if sustained for greater than a year, may lead to permanent AF.

Left Atrial Appendage (LAA) and Nonvalvular Atrial Fibrillation

The loss of mechanical efficiency during AF leads to insufficient contraction in the left atrium (LA) (Ostermayer 2005). Stagnation of blood flow in the LA leads to hypercoagulability and thus increased risk for thrombus formation in the left atrium or left atrial appendage. Approximately 90% of all thrombi in subjects with nonvalvular AF forming in the LA originate in the LAA (Blacksheer 1996). The thrombus formation, in turn, exposes the subject to thromboembolic events. Approximately 6% of embolic events result in peripheral embolism as opposed to ischemic stroke (Go 2003).

Echocardiographic risk factors for LAA thrombus formation include echocardiographic evidence of decreased LAA flow velocity and spontaneous echo contrast (SEC) within the LA and LAA (Stollberger 2003 and Miller 1993). The normal flow pattern of the LAA is the ejection of blood from the appendage following atrial contraction at a velocity greater than 40cm/s

(Alizadeh 2006). Agmon et al (1999), found that the relative risk reduction of ischemic stroke was 2.6 times greater in subjects with LAA flow velocities <20cm/s than those with higher LAA velocities.

Ischemic strokes in subjects with AF have been found to cause major deficits as compared to ischemic strokes in subjects with carotid disease. Subjects with AF have also been found to have silent infarcts in the SPINAF study in which a CT scan was performed both initially and then again at the end of the follow-up period (Ezekowitz 1995).

Nonvalvular AF subjects can be further assessed to determine the risk of stroke based on the existence of independent risk factors. In a study by Gage et al (2001), the $CHADS_2$\ index was found to be the most accurate in predicting the risk of stroke in subjects with AF. The $CHADS_2$ score assigns one point each for the presence of congestive heart failure, hypertension, age greater than 75, and diabetes mellitus, and two points for history of stroke or TIA. The study found that AF subjects who were not treated with antithrombotics had an increased risk of stroke from 1.5% to 18.2% based on the score of 1 and 6 respectively. A second study reviewed outcome data (11,526 subjects) in a large primary care setting and confirmed that thromboembolic risk increases progressively with $CHADS_2$ score. The study also noted that oral anticoagulation with warfarin reduces risk of stroke in most subjects with the exception of those at lowest risk ($CHADS_2$ score of zero) and highest risk ($CHADS_2$ of ≥5) (Go et al, 2003).

STATISTICS

An estimated 2.3 million people in North America and 4.5 million people in the European Union have paroxysmal or persistent AF (Go 2001). The estimated prevalence of AF is 0.4% to 1% in the general population, increasing with age to 8% in those older than 80 (Vural 2005 and Frost 2000).

Atrial fibrillation is responsible for 15% to 20% of ischemic stroke (Crystal 2004). 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 subjects with nonvalvular AF is approximately 5% per year in subjects under 65 years and it increases to over 8% per year in subjects over 75 (AF Investigators Arch Intern Med 1994). Based on risk factors and treatment or the lack thereof the risk of stroke can be as high as 18.2% per year in select subjects (Gage 2001).

CURRENT TREATMENT OPTIONS

Medical Management for AF

Treatment for AF includes both pharmacological and/or interventional based on the subject's type of AF. Anti-arrhythmic or rate control drugs are commonly used to treat subjects with AF. Medical interventions include electrical cardioversion, cardiac catheter ablation, atrial defibrillators, pacemakers, or maze procedure. Regardless of the type of treatment modality chosen for rate or rhythm control, the need for anticoagulation therapy should still be based on stroke risk and not on whether proper heart rhythm is maintained (Fuster and Ryden 2006).

The evidence indicates that both OAC and aspirin are effective for prevention of systemic embolism in subjects with nonvalvular AF (Petersen 1989, SPAF 1991, BAATAF 1990,

Connolly 1991, Ezekowitz 1992, EAFT 1993). In a meta-analysis conducted by Anderson et al (2008), warfarin was found to be superior to ASA and placebo in reducing the risk of both stroke and systemic embolism in subjects with nonvalvular AF. Hart et al (2007) reported that adjusted dose warfarin reduces stroke by 64% (six trials) and antiplatelet agents reduce stroke risk by 22% (8 trials). The study also reported the risk of intracranial hemorrhage was doubled with adjusted dose warfarin compared with aspirin, although the absolute risk increase was small (0.2% per year) and all-cause mortality was substantially reduced (26% [CI, 3% to 43%]) by adjusted-dose warfarin vs. control. Subjects are often poorly compliant with anticoagulation, and anticoagulants are contraindicated in selected subsets of subjects.

More recently, new drugs have been developed with less dietary and pharmacological interactions and less stringent requirements for frequent INR monitoring. Major trials such as RE-LY and ROCKET AF have demonstrated that dabigatran and rivaroxaban are non-inferior to warfarin in the prevention of stroke and systemic embolism. For example in the RE-LY study, the overall annual major bleeding rate with dabigatran was lower than with warfarin (2.71%/3.11% for 110/150 mg dabigatran vs. 3.36% for warfarin) but GI bleeding for both doses of dabigatran was (non-significantly) higher than for warfarin (1.12%/1.51% for 110/150 mg dabigatran vs. 1.02% for warfarin) (Connolly et al 2009, Patel et al 2011). In view of the bleeding associated with warfarin and new OAC drugs, especially, patients who are at high risk for stroke as well as for bleeding may benefit from alternative stroke prevention therapies.

Surgical Closure of the LAA

Surgical removal/closure of the LAA has been performed in subjects undergoing mitral valve surgery or the maze procedure. Garcia-Fernandez et al (2003) completed a retrospective analysis of 58 subjects who underwent ligation of the LAA during mitral valve surgery. The study reported a residual shunt rate of 10% in these subjects. Residual shunting correlated with an increased risk of late embolism. However, in a prospective study conducted by Almahameed et al (2007) the rate of thromboembolism post LAA exclusion was not statistically significantly less than subjects treated with warfarin.

Percutaneous Closure of LAA

LAA obliteration is now feasible via a percutaneous approach. A device to reduce the risk of embolization from LAA thrombi, especially when associated anticoagulation is a relative or absolute contraindication, would be a desired option in such subjects. Studies comparing investigational percutaneous LAA occlusion techniques with traditional anticoagulation are ongoing.

Sievert et al (2002) reported on 15 subjects with chronic AF and a contraindication to warfarin implanted with the PLAATO Device (manufactured by *ev3)* for LAA occlusion. Complete closure was observed in all subjects and there were no reported complications.

Ostermeyer et al (2005) also reported preliminary results with the PLAATO Device. Successful LAA occlusion was achieved in 108/111 (97.3%) subjects.

Sick et al (2007) reported the early results of a small feasibility study performed with the WATCHMAN System (manufactured by Atritech). Sixty-six (66) patients were enrolled at centers

in both the U.S. and internationally and included patients who had chronic or paroxysmal atrial fibrillation and a $CHADS_2$ score of one or greater. Two (2) patients experienced systemic embolic events which were a safety endpoint in the study and 4 patients developed thrombus on the device.

A multi-center, prospective, randomized study (PROTECT AF), comparing the WATCHMAN device to long-term warfarin therapy, demonstrating the treatment arm is non-inferior to the control arm completed enrollment in June 2008. The primary endpoint of this study is to characterize the rates of all stroke, systemic embolism and cardiovascular death in patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation and are eligible for warfarin therapy. PROTECT AF demonstrated that LAA closure is non-inferior to warfarin for all-cause stroke and all-cause mortality, reducing stroke and all-cause death by 32% compared to warfarin. Although the non-inferiority endpoint was met, the results were not statistically significant for superiority.

Currently, the PREVAIL (Prospective Randomized EVAluation of the Watchman LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy) trial is enrolling AF patients at risk for stroke to be randomized to either anticoagulation therapy or implantation of the WATCHMAN device. The primary endpoint is the occurrence of stroke, cardiovascular death and systemic embolism. The study plans for enrollment of 475 patients who will be followed for 5 years.

Recent experience with the ACP device in Europe includes 204 high risk subjects enrolled in the ACP EU Prospective Observational Study. Subjects' risk factors for stroke (mean $CHADS_2$: 2.6) included hypertension and age > 75 years. Furthermore, 80 subjects had a previous stroke or TIA prior to implantation of the ACP. In 80% of the subjects, percutaneous LAA occlusion was indicated by a high bleeding risk and 3.9% were on active anticoagulation therapy at the time of enrollment. High closure success rates of 99.5% were found immediately after successful implantation and at discharge and remained high at six months post implant (98.9%).

2.2 RATIONALE

The rationale for the ACP clinical investigation is to potentially offer a device that is safe and effective in preventing thrombus from migrating from the left atrial appendage (LAA) in subjects who have nonvalvular atrial fibrillation and is a potential alternative to long-term anticoagulation therapy.

2.3 NAME AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The AMPLATZER Cardiac Plug (ACP) is a transcatheter, self-expanding device constructed from a nitinol mesh and polyester patch. The ACP consists of a lobe and a disc connected by a central waist. It is available in eight diameter sizes (16, 18, 20, 22, 24, 26, 28, and 30 mm). The lobe has stabilizing wires to improve device placement and retention. The device has threaded screw attachments at each end for connection to the delivery and loading cable. The device also has radio-opaque markers at each end and at the stabilizing wires. The ACP is designed to prevent thrombus embolization from the left atrial appendage (LAA) in subjects who have nonvalvular atrial fibrillation.

2.4 LITERATURE AND CLINICAL DATA

A complete bibliography is provided in Section 2.30.

2.5 ELIGIBILITY CRITERIA

A subject is eligible to participate in the study if he/she meets all inclusion criteria and meets no exclusion criteria. A screening log will be kept at each site to document subjects who fail to meet the entry criteria or refuse to participate in the clinical trial. All screened subjects will be documented on the screening Case Report Form (CRF).

Inclusion Criteria

1. Subject must have a documented history of paroxysmal, persistent or permanent nonvalvular atrial fibrillation (documentation must include an electrocardiogram (EKG), Holter, or event recorder)
2. Subject must be ≥18 years of age
3. Subject must be on warfarin therapy or dabigatran therapy* for a minimum of one month immediately prior to enrollment. For those subjects who are on warfarin therapy, at least two International Normalized Ratios (INRs) between 2-3 must be achieved during this time. Subjects whose INR is not in the target range may return for rescreening once target INR is achieved.
4. Subject must be eligible for long term warfarin or dabigatran therapy*

   **Dabigatran dosing (75 mg or 150 mg bid) should be in accordance with its approved directions for use*
5. Subject must have a $CHADS_2$ score of 2 or greater (score all criteria according to the following chart)

$CHADS_2$ Risk Criteria	**Score**
Prior stroke or TIA	2
Age >75 y	1
Hypertension	1
Diabetes mellitus	1
Heart Failure	1

Exclusion criteria

1. Subject who requires warfarin or dabigatran for a condition other than AF
2. Subject who is on clopidogrel or another P2Y12 platelet inhibitor such as prasugrel or ticagrelor (subject may be rescreened after 7 days)
3. Subject with an New York Heart Association (NYHA) classification equal to IV
4. Subject with an implanted atrial septal defect (ASD) device or patent foramen ovale (PFO) device

5. Subject with a history of surgical ASD or PFO repair
6. Subject with a history of stroke and unrepaired PFO
7. Subject with aortic valve stenosis with valve area <1cm^2
8. Subject with mitral valve stenosis with valve area <1.5cm^2
9. Subject with aortic or mitral valve regurgitation of Grade 2+ or greater (Grade 2+ is defined as jet length ≥ 1.5 and <3.0cm and jet area ≥ 1.5 and <3.0 cm^2)
10. Subject with mitral or aortic prosthetic valve
11. Subject with left ventricular ejection fraction (LVEF) of ≤ 30
12. Subject with evidence of pericardial effusion
13. Subject with complex atheroma with mobile plaque of the descending aorta and/or aortic arch
14. Subject with evidence of an intracardiac thrombus (subject can be rescreened after appropriate thrombolytic therapy and confirmed absence of thrombus)
15. Subject with carotid disease as assessed by the investigator, requiring treatment, which includes revascularization and/or medical treatment
16. Subject with LAA landing zone that measures with a width <12.6mm or >28.5mm (via TEE)
17. Subject without sufficient space (minimum 10 mm) distal to the LAA orifice to accommodate insertion of the dilator and sheath (via TEE)
18. Subject with active infection or active endocarditis
19. Subject with history of acute or recent myocardial infarction (MI) or unstable angina (within six months from the date of signing informed consent)
20. Subject with a history of hemorrhagic or aneurysmal stroke
21. Subject with a history of stroke and a Modified Rankin Score of ≥3
22. Subject with a history of coronary artery bypass graft (CABG) surgery (within six months from the date of signing informed consent)
23. Subject who is/or wishes to participate in any other concurrent clinical trial that may confound the results of this study (i.e. AF drug study, RF ablation study for AF)
24. Subject who has a planned cardioversion within 30 days post-device implantation
25. Subject who has uncontrolled AF (e.g., resting heart rate>110 bpm**)**
26. Subject who has transient AF secondary to surgical procedure or RF ablation
27. Subject who has a history of thrombosis occurring at a young age (i.e., less than 40 years of age)
28. Subject who has a history of idiopathic or recurrent venous thromboembolism
29. Subject who has a history of thrombosis at an unusual site (cerebral veins, hepatic veins, renal veins, Inferior Vena Cava, mesenteric veins)

30. Subject who has a history of recurrent thrombosis while adequately anticoagulated
31. Subject who has uncontrolled hypertension (SBP >180 mm Hg or DBP >100 mm Hg)
32. Subject who has thrombocytopenia (<100,000 platelets/mm^3) or anemia with Hb of< 10 g/dl
33. Subject with a history of previous radio frequency (RF) ablation for atrial fibrillation
34. Subject who has an absolute or relative contraindication to both warfarin and dabigatran
35. Subject who has an absolute or relative contraindication to aspirin
36. Subject who is on medication which may interact with aspirin, warfarin, or dabigatran
37. Subject who is on or intends to be on rivaroxaban
38. Subject who is on aspirin therapy dosage greater than 81 mg/day at time of enrollment (Subject may be rescreened after 7 days)
39. Subject with history of deep vein thrombosis (DVT) or pulmonary embolism within six months from the date of signing informed consent
40. Subjects with an estimated serum creatinine clearance of ≤ 30 ml/min (Cockcroft and Gault)
41. Subject with inferior vena cava (IVC) filter
42. Subject with a body mass index (BMI) ≥40
43. Subject with known malignancy or other illness where life expectancy is less than two years
44. Subject who is pregnant or desires to become pregnant during the course of the trial
45. Subject or legally authorized representative who is unable to provide informed consent
46. Subject who will not be able to be followed for the duration of the clinical trial
47. Subject with any medical disorder that would interfere with completion or evaluation of clinical trial results

2.6 SUBJECT PARTICIPATION AND INFORMED CONSENT

Subjects or their legally authorized representative will be informed of the study and invited to participate. Informed consent must be obtained from each subject or legally authorized representative prior to any clinical investigation participation (including the Baseline Phase), using the Informed Consent Form (ICF) HIPAA authorization form or any other applicable permission form(s) required by law approved by the IRB. The subject/legally authorized representative will be provided with a copy of the Informed Consent Form and HIPAA authorization form or any other applicable permission form(s) required by law and its content will be reviewed verbally with the subject/legally authorized representative by the study investigator or authorize delegate, allowing adequate time for review and questions. The study investigator or authorized delegate will fully explain to the subject or legal representative the

nature of the research, clinical investigation procedures, anticipated benefits, and potential risks of participation in the clinical investigation. All information pertinent to the study shall be provided in writing and in native, non-technical language that is understandable to the subject or subject's legally authorized representative.

Once the subject/legally authorized representative has read and understands the Informed Consent Form and HIPAA authorization form or any other applicable permission form(s) required by law, he/she will indicate his/her willingness to participate in the study by signing the form(s).

If a subject or legally authorized representative is unable to read or write, the informed consent shall be obtained through a supervised oral process. An independent witness shall be present throughout the process. Upon completion of the supervised oral process, the Informed Consent Form, HIPAA authorization form or any other applicable permission form(s) required by law must be signed and dated by the subject or legal representative and by the person obtaining the consent attesting that the information was accurately explained and that informed consent was freely given.

The informed consent process will be fully documented by the investigator or authorized delegate in the medical record and include the date on which the consent was obtained. The original signed consent form HIPAA authorization form or any other applicable permission form(s) required by law will be retained in the subject's study records. A copy of the signed informed consent HIPAA authorization form or any other applicable permission form(s) required by law will be provided to the subject or legal representative and a copy placed in the subject's medical record. Following signing of the consent and HIPAA authorization form or any other applicable permission form required by law the subject's eligibility for the study will be determined.

If new information becomes available during the study that can significantly affect a subject's future health and medical care, or willingness to continue in the study, that information will be provided to the subject(s) in writing.

2.7 ENROLLMENT

Subjects will be considered enrolled d in the study after informed consent and HIPAA authorization form or any other applicable permission form required by law has been signed and the subject has been randomized. The following terms will be used to describe potential study participants who do not fully implement the assigned therapy:

- **Non-Consented Screen Failure** - Subject who are screened to participate in the study but do not sign the Informed Consent Form and HIPAA authorization form or any other applicable permission form required by law. These subjects will not be considered enrolled in the study.

- **Consented Screen Failure** - Subject/legally authorized representative who signs the Informed Consent Form and HIPAA authorization form or any other applicable permission

form required by law, but the subject does not meet eligibility criteria. These subjects will not be considered enrolled in the study.

- **Intent-to-Treat** - A subject will be considered part of the intent-to-treat analysis population as long as she/he is randomized into the study, with no adjustment made for whether the device was implanted, compliance with treatment, or events occurring after randomization. These subjects will be enrolled in the study and included in the primary endpoint analysis.

2.8 SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

A subject may be considered discontinued from the study if (including but not limited to):

- Subject/legally authorized representative withdraws consent;
- Subject is lost to follow-up;*
- Subject dies;
- Subject completes the study-required follow-up;
- Study management decision by Sponsor to end the study as a whole or just at a particular study location;
- Subject discontinued due to medical necessity by investigator or upon request of a regulatory body; or
- Study site prematurely terminates its participation in the study;

**The following actions will be undertaken prior to categorizing a subject as lost to follow-up. Two attempts will be made to contact the subject via phone, email, or mail. If no response is obtained, a registered or certified letter will be sent to the subject as a last means of contact.*

2.9 BASELINE EVALUATION

Informed consent will be obtained from the subject/legally authorized representative prior to conducting any study related activities.

The following baseline testing will be performed:

1. Medical History
2. Physical exam (PE)
3. National Institute of Health (NIH) Stroke Scale - All personnel conducting any study required NIHSS evaluations are required to have received training and certification per nationally accepted guidelines such as American Stroke Association, or American Academy of Neurology, or National Institute of Neurological Disorders and Stroke
4. Modified Rankin
5. Magnetic Resonance Imaging (MRI) of the head/brain must include FLAIR, DWI, ADC maps, and gradient echo (GRE) among other sequences.

Note: If medically contraindicated to MRI, subjects should have a Computed Tomography (CT) of the head performed

6. $CHADS_2$ assessment
7. Pregnancy test (required only for females of child bearing potential)
8. 12 Lead ECG
9. Transesophageal echocardiography (TEE) - If thrombus is detected, subject may be rescreened by TEE, after 12 weeks of anticoagulation therapy for consideration of device placement following documentation of absence of intracardiac thrombus
10. INR assessment (only for subjects who are warfarin therapy) – Subjects on warfarin whose INR is not in the target range (at baseline) may return for rescreening once target INR is achieved. During rescreening, subjects must demonstrate two consecutive INRs within the target range (2-3).
11. Medication Determination and Assessment

    OMT and concomitant use of aspirin therapy prior to randomization:

    The principal investigator should determine appropriate OMT and need for concomitant aspirin therapy as medically indicated for each subject. Subjects must remain on the assigned OMT (warfarin or dabigatran with or without concomitant aspirin therapy) for one month prior to enrollment (defined as time of informed consent, HIPPA and randomization). Should the subject's medical condition change, the Principal Investigator may make changes in the OMT and / or aspirin therapy regimen as needed; however, the subject must take the newly assigned OMT for a minimum of one month prior to randomization. Re-screening rules pertaining to both inclusion and exclusion criteria will apply. All medication changes and accompanying rationale must be documented on the medication log.
12. Hematology Parameters
    a. Hemoglobin
    b. Hematocrit
    c. Serum Creatinine
    d. Platelets
13. Coagulation parameters
    a. Fibrinogen antigen
    b. Quantitative D-dimer
    c. Von-Willebrand antigen
    d. Thrombin-Antithrombin complex
    e. Prothrombin fragment 1.2
    f. Homocysteine
    g. tPA antigen
    h. PAI-1 antigen
14. Neurological Symptoms Interview

15. Quality of Life Interview (EQ-5D-3L)

2.10 RANDOMIZATION

After subject has signed informed consent, HIPAA authorization form or any other applicable permission form required by law and meets all inclusion and none of the exclusion criteria, the subject will be randomized.

A medical management decision, treatment with warfarin or dabigatran* will be made by the principal investigator prior to randomization. The principal investigator must document the optimal medical therapy including the concomitant use of aspirin prior to randomization on the baseline case report form. Subjects will be randomized to either the device arm or the control arm respectively in a 2:1 ratio. Randomization will be stratified by study center, oral anticoagulant therapy (warfarin or dabigatran), and baseline concomitant aspirin usage. Randomization into the concomitant aspirin strata will be capped at 20% of total study enrollment.

**Dabigatran dosing (75 mg or 150 mg bid) should be in accordance with its approved directions for use.*

Subjects in both groups will be assigned a subject ID number at the time of consent. Subjects who are randomized to the device arm must follow the pre-procedure care instructions (Section 2.11.1). The implant procedure must be performed within fourteen (14) days of randomization.

Subjects who are randomized to the control arm must continue taking the OMT that has been assigned by the principal investigator until a primary endpoint is met or the study is completed. Those subjects on warfarin should maintain an INR between 2-3 with adjustment of dosage as needed. Discontinuation of designated OAC (warfarin, dabigatran) or addition of other anticoagulants or antiplatelet medications is not allowed unless medically necessary.

2.11 AMPLATZER CARDIAC PLUG IMPLANTATION PROCEDURE

2.11.1 PRE PROCEDURE CARE

a. <u>Bridge regimen for subjects on warfarin</u>

- Stop warfarin 4 days prior to the day of procedure
- Start Lovenox 2 days prior to the day of procedure at 1 mg/kg subcutaneously every 12 hours for 2 days (subjects with renal dysfunction may require dosage adjustment as determined by the physician)
- On day of the procedure do <u>not</u> administer Lovenox or warfarin

Example: Day 5 is day of procedure:

- Day 1 – stop warfarin
- Day 2 – no medications (Lovenox or warfarin)
- Day 3 – begin Lovenox at 1 mg/ kg subcutaneously every 12 hours

- Day 4 – continue Lovenox at same dosage
- Day 5 - procedure day, no Lovenox (or warfarin)

INR Test

INR must be tested within 24 hours prior to the procedure. An INR should be ≤1.5 in order to proceed with the device implantation procedure.

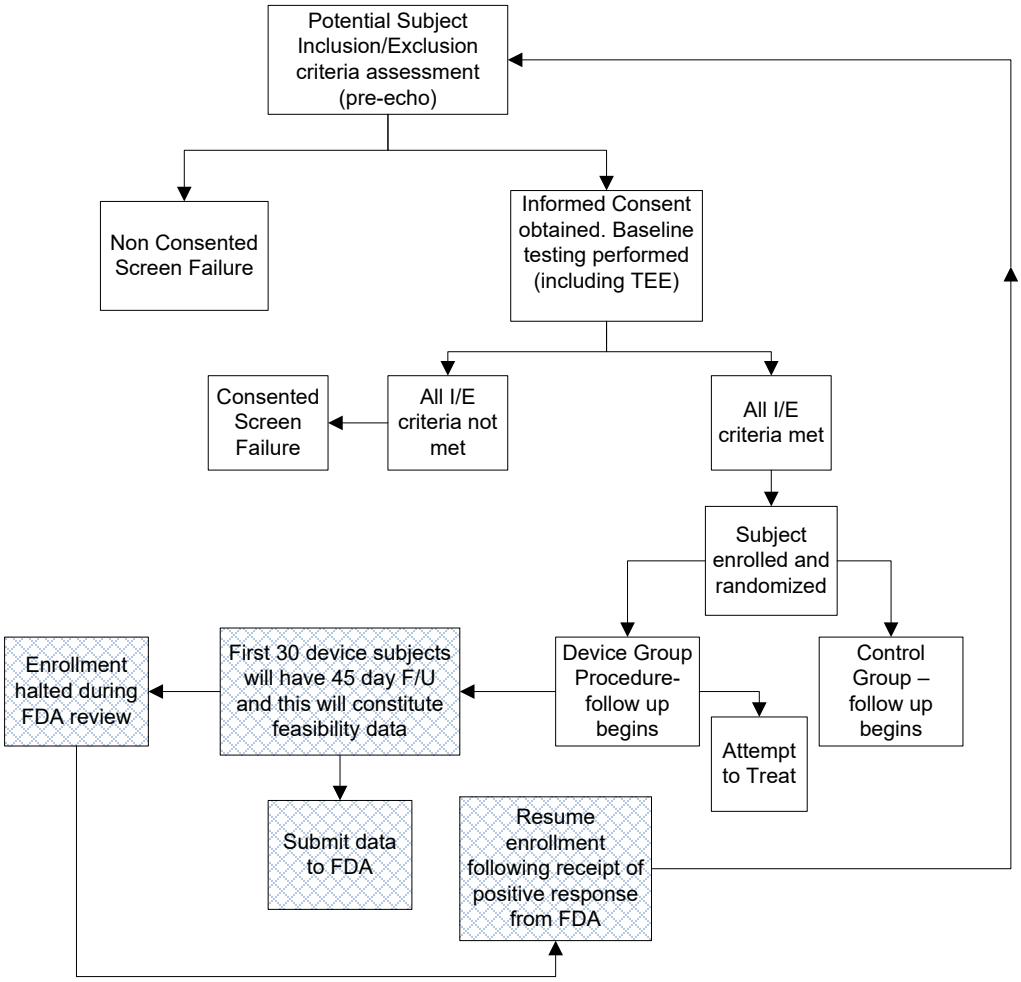
b. Bridge regimen for subjects on dabigatran

Discontinue dabigatran 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures (see dabigatran prescribing information by manufacturer).

2.11.2 PROCEDURE (RANDOMIZED TO DEVICE ARM)

- Procedure must be performed within 14 days from the date of randomization.
- Procedure will be performed under TEE and angiographic guidance.
- On an angiogram assessment, if a subject has an LAA landing zone measured with a width of less than 12.6mm (at its widest point) or greater than 28.5mm at its widest point, the subject will not proceed with device implantation. These subjects will be considered intent to treat.
- On an angiogram assessment, if a subject has insufficient space (minimum 10 mm) distal to the LAA orifice to accommodate insertion of the dilator and sheath, the subject will not proceed with device placement. These subjects will be considered as intent to treat.
- Refer to the Instructions for Use for the recommended device size, delivery sheath selection, and ACP implantation procedure.

2.11.3 ENROLLMENT SCHEME



This section pertains to the feasibility phase which is complete

2.11.4 POST PROCEDURE CARE THROUGH HOSPITAL DISCHARGE

2.11.4.1 Post procedure care for the device arm (for subjects who are randomized to the device arm and receive the device) is to be as follows:

- Subjects must be kept overnight (24 hour stay) for observation.
- Subjects must return to OMT (assigned by the principal investigator at time of randomization) as described below.

2.11.4.1.1 Device Subjects Assigned to Warfarin

- Subjects will be discharged from the hospital on warfarin (adjustment of dosage to keep an INR between 2-3 must be made during the study while subjects are on warfarin).Until the subject's INR is between 2 and 3, Lovenox 1mg/kg subcutaneously twice a day should be administered starting within 24 hours after the procedure.
- INR testing should commence 2-3 days after the initiation of warfarin therapy and be tested frequently until a stable dose/INR has been achieved and then at least every 4 weeks subsequently.

2.11.4.1.2 Device Subjects Assigned to Dabigatran

- Dabigatran therapy* should be re-started after wound hemostasis is satisfactory in accordance with its approved directions for use). Subjects will be discharged from the hospital on dabigatran. Dabigatran dosing* should be in accordance with its approved directions for use.
  **Dabigatran dosing (75 mg or 150 mg bid) should be in accordance with its approved directions for use*.

2.11.4.2 Post procedure care for subjects who are randomized to the device arm but do not receive a device (or device is removed) is required as follows:

2.11.4.2.1 Device Subjects Assigned Warfarin

- Subjects are discharged from the hospital on warfarin and will continue to take warfarin throughout the duration of the clinical trial (adjustment of dosage to keep an INR between 2-3 must be made during the study while subjects are on warfarin), or until a primary endpoint is met or the study is completed.
- For attempt to treat subjects who stopped warfarin, until the subject's INR is between 2 and 3, Lovenox 1mg/kg sq, twice a day, should be administered starting the day after the procedure.
- INR testing should commence 2-3 days after the initiation of warfarin therapy and be tested frequently until a stable dose/INR has been achieved and then at least every 4 weeks subsequently.

- Discontinuation of warfarin or addition of other anticoagulants or antiplatelet medications is not allowed unless medically necessary.

2.11.4.2.2 Device Subjects Assigned to Dabigatran

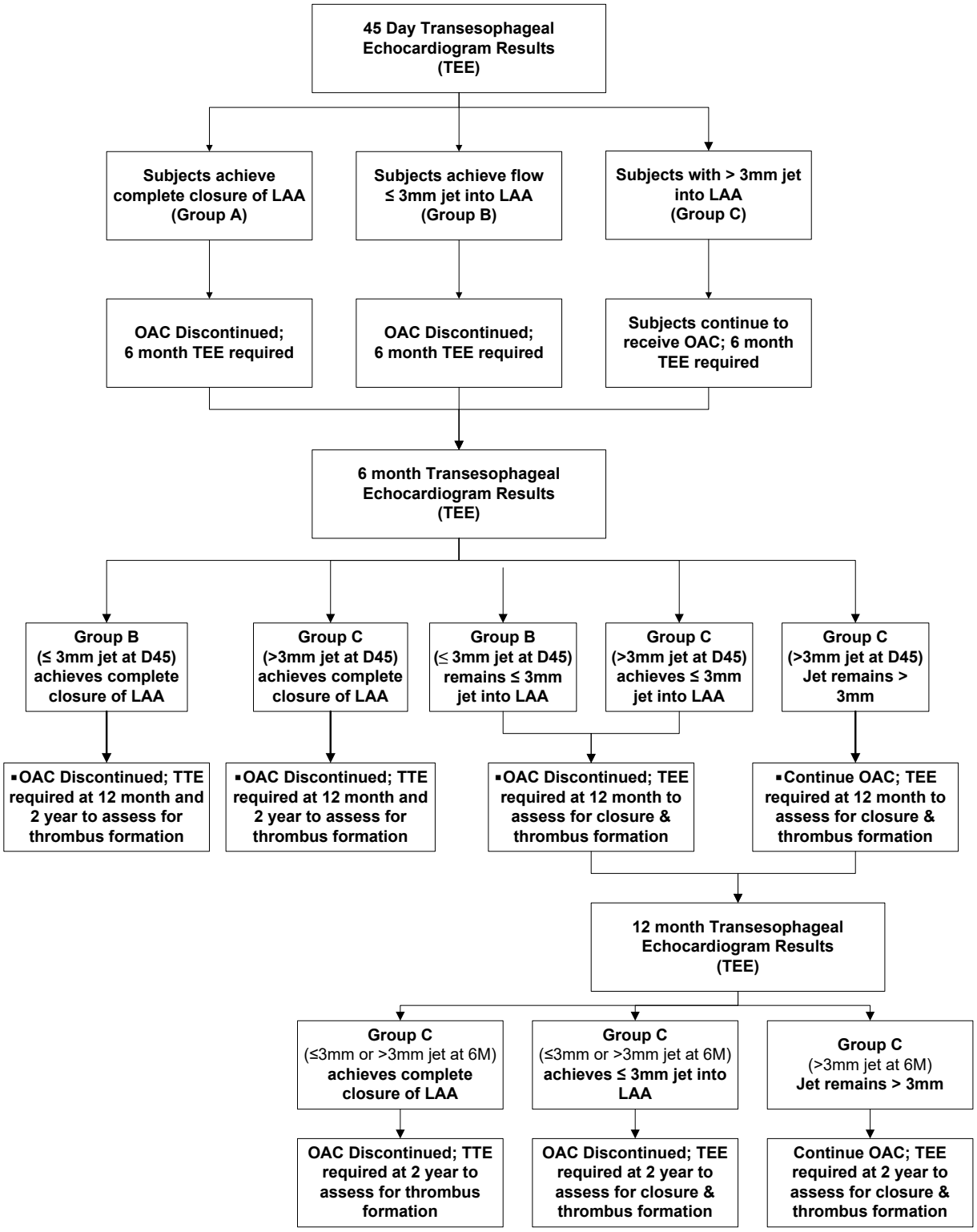
- Subjects will be discharged from the hospital on dabigatran and will continue to take dabigatran throughout the duration of the clinical trial or until a primary endpoint is met or the study is completed.
- Discontinuation of dabigatran or addition of other anticoagulants or antiplatelet medications is not allowed unless medically necessary.

2.12 FOLLOW-UP REQUIREMENTS (REFER TO APPENDIX D)

1. Refer to section 2.12.1, 2.12.2, and 2.12.3.
2. Adverse events for all randomized subjects will be collected from the time of informed consent through discontinuation or end of the study.
3. For subjects randomized to control arm and those subjects who are randomized to device arm but do not undergo an implant attempt, follow-up windows are calculated based on the day of randomization. For subjects who undergo an implant attempt and/or receive the device, follow-up windows are calculated from the date of procedure. Subjects who are on warfarin should maintain an INR between 2-3 INR levels must be documented on an INR log. (REFER TO APPENDIX D)
4. Post procedure TEE requirements for the device arm subsequent to hospital discharge: Refer to TEE flow chart below.
5. For subjects randomized to the device arm, once OAC therapy is discontinued, aspirin (325 mg daily) must be started and continued throughout the duration of the trial. If the subject is already on aspirin 81 mg daily, increase dosage to 325 mg daily.
6. Bacterial endocarditis prophylaxis should be carried out for at least six months post procedure (see Appendix C).
7. For subjects who receive the device, a telephone call must be scheduled 3 months (+/- 10 days) post discontinuation of OAC therapy to inquire if subjects have restarted OAC therapy. Telephone call will be documented as an Interim Visit.
8. If during a phone follow-up, a serious adverse event is reported or a response of "Yes" or "Don't know" to any question on Neurological Symptom Interview is elicited, an in-person interim office visit is required.
9. If asymptomatic cerebral hemorrhage is detected through imaging, please note that there are no standardized clinical guidelines or treatment recommendation for the use of antithrombotic therapy based on MR Imaging findings. These subjects in both groups (device and medical management) should be managed per institutional or investigator standard of care.
10. As part of the health economic and quality of life sub-study, hospital bills of enrolled subjects will be collected up to 2 years or until the study is completed. (REFER TO APPENDIX D)

Transesophageal Echocardiogram (TEE) Imaging Schedule

Flow Diagram for Subjects who are randomized to the device arm



2.12.1 ASSESSMENT AND FOLLOW-UP SCHEDULE; SUBJECTS WHO RECEIVE THE DEVICE (REFER TO APPENDIX D)

	Procedure	Pre-discharge (+ 1 day)	45 days (+/-5 days)	3 Month (+/- 10 days) Post OAC Discontinuation Phone Visit [8]	6 months (+/- 30 days)	12 months (+/-30 days)	18 months (+/-60 days)	2 years (+/- 60 days)	Annually thereafter (+/- 60 days) phone visit [4]
Physical Exam		X	X		X	X	X	X	
Neurological Symptoms Interview			X		X	X	X	X	X [5]
Urine Pregnancy Test	X[1]								
12 lead Electrocardiogram		X	X		X	X	X	X	
2-D Color Flow Doppler Transthoracic Echo (TTE)		X				X [6]		X [6]	
Transesophageal Echocardiogram (TEE)	X		X		X	X [6]		X [6]	
MRI of head/brain [7]						X		X	
Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Medication Assessment [2]	X	X	X	X	X	X	X	X	X
INR Assessment [3]									
Quality of Life Assessment(s)						X		X	

[1]Urine pregnancy test must be done within 24 hours prior to the procedure (for female subjects of childbearing potential)

[2]Review and record all and any changes to antiarrhythmic and antiplatelet medications

[3]INR must be tested within 24 hours prior to the procedure (for those subjects on warfarin). Post procedure- INR testing should commence 2-3 days after the initiation of warfarin therapy and be tested frequently until a stable dose / INR has been achieved and then at least every 4 weeks subsequently. Subjects are recommended to maintain a target INR between 2-3 while they are on warfarin

[4]Follow-up visits after 2 years will be via telephone

[5]If during a telephone visit, an SAE is reported or a response of **Yes or Don't know** to any question on the Neurological Symptoms Interview is elicited an in-person interim office visit is required

[6]Refer to flowchart above

[7]MRI must include FLAIR, DWI, ADC maps, and GRE among other sequences. If subject is medically contraindicated to MRI, a CT of the head must be performed. If asymptomatic cerebral hemorrhage is detected through imaging, please note that there are no standardized clinical guidelines or treatment recommendation for the use of antithrombotic therapy based on MR Imaging findings. These subjects in both groups (device and medical management) should be managed per institutional or investigator standard of care.

[8] This phone visit must be performed 3 months after a subject stops taking OAC (Note: OAC must be discontinued once no flow or ≤3mm jet into the LAA (via TEE) has been demonstrated

One week equals 7 days. One month = 30 days. One year= 365 days

2.12.2 ASSESSMENT AND FOLLOW-UP SCHEDULE: CONTROL SUBJECTS AND SUBJECTS RANDOMIZED TO THE DEVICE AND DO NOT RECEIVE THE DEVICE

	Procedure[2]	Pre-discharge[2] (+ 1 day)	45 days (+/-5 days)	6 months (+/- 30 days)	12 months (+/-30 days)	18 months (+/-60 days)	2 years (+/- 60 days)	Annually thereafter (+/- 60 days phone visit)[5]
Physical Exam		X	X	X	X	X	X	
Neurological Symptoms Interview			X	X	X	X[6]	X	X[6]
Urine Pregnancy Test	X[1]							
12 lead Electrocardiogram		X	X	X	X	X	X	
Transthoracic Echocardiogram (TTE)[2]		X						
Transesophageal Echocardiogram (TEE)2	X							
MRI of head/brain[7]					X		X	
Adverse Event Assessment	X	X	X	X	X	X	X	X
Medication Assessment[3]	X	X	X	X	X	X	X	X
INR Assessment[4]								
Quality of Life Assessment(s)					X		X	

[1]For device attempt female subjects of childbearing potential. Must be performed within 24 hours prior to the procedure

[2]For device attempt subjects

[3]Review and record all changes to antiarrhythmic and antiplatelet medications

[4]INR must be tested with 24 hours prior to the procedure for device attempt subjects only (for those subjects on warfarin). INR testing should commence 2-3 days after the initiation of warfarin therapy and be tested frequently until a stable dose/INR has been achieved and then at least every 4 weeks subsequently. Subjects are recommended to maintain a target INR between 2-3 while they are on warfarin

[5]Follow-up visits after 2 years will be via telephone

[6]If during a telephone visit, an SAE is reported or a response of **Yes or Don't know** to any question on the Neurological Symptoms Interview is elicited an in-person interim office visit is required

[7]MRI must include FLAIR, DWI, ADC maps, and GRE among other sequences. If subject is medically contraindicated to MRI, a CT of the head must be performed. If asymptomatic cerebral hemorrhage is detected through imaging, please note that there are no standardized clinical guidelines or treatment recommendation for the use of antithrombotic therapy based on MR Imaging findings. These subjects in both groups (device and medical management) should be managed per institutional or investigator standard of care.

One week equals 7 days. One month = 30 days. One year = 365 days

2.12.3 ASSESSMENT AND FOLLOW-UP SCHEDULE: SUSPECTED STROKE, TIA, OR PERIPHERAL THROMBOEMBOLISM

If stroke, TIA, or peripheral thromboembolism is suspected at any time after *randomization,* further evaluation should be performed within 14 days from the date the site becomes aware of the event. For a suspected stroke or TIA, a MRI or CT must be performed within 10 days of the event occurrence. For peripheral thromboembolism, evaluate per physician standard of care. All source documentation for primary endpoints must be sent in to AGA Medical as soon as possible.

Suspected Stroke or TIA Assessment[1]

Neurologic Assessment • NIH Stroke Scale[2] • Modified Rankin
MRI (or CT if medically contraindicated to MRI) must be performed within 10 days of event (should include FLAIR, DWI, ADC maps, among other sequences) • Submit Report and Films to AGA Medical
Transesophageal Echo[3] • Submit Report and Videotape or DICOM CD to AGA Medical
Follow-up Form
Adverse Event Form

[1]All subjects are followed until completion of trial

[2]All personnel conducting any study required NIHSS evaluations are required to have received training and certification per nationally accepted guidelines such as American Stroke Association, or American Academy of Neurology, or National Institute of Neurological Disorders and Stroke

[3]TEE is required only on device subjects with confirmed stroke

Peripheral Thomboembolism[1]

Follow-up Form
Adverse Event Form

[1]All subjects are followed until completion of trial

2.13 ADVERSE EVENTS

2.13.1 UNANTICIPATED ADVERSE DEVICE EFFECT

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 investigational plan, including a supplementary plan or application, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3 (s)).

2.13.2 ADVERSE EVENTS

Adverse Events will be classified as Serious Adverse Event, Adverse Event, or Observations.

Serious Adverse Event - is defined as those adverse events resulting in the following: death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospital stay, persistent or significant disability/incapacity, or medically significant event.

Serious adverse events are further classified as either device- or procedure-related.

Adverse Event - is defined as an event which does not meet the definition of a serious adverse event but is still an undesirable clinical occurrence and is a negative change from baseline, whether or not device related

- **Observation** - an observation is a subset of adverse events that are usually transient and do not require clinician prescribed intervention. The event does not generally interfere with usual activities of daily living (e.g. fatigue, common cold, strained muscle).

Potential Anticipated Adverse Events include but are not limited to:

- **Air embolus** – symptomatic event resulting from introduction of air into circulatory system
- **Allergic contrast reaction** – idiosyncratic reaction to contrast used in imaging
- **Allergic drug reaction** – idiosyncratic reaction to drugs
- **Allergic device reaction** - idiosyncratic reaction to the device implanted
- **Anemia-** a decrease in the number of red blood cells (RBC's) or hemoglobin, resulting in a lower ability for the blood to carry oxygen to body tissues
- **Anesthesia reaction** – undesired reaction to anesthetic agent
- **Arrhythmia** – cardiac rhythm disturbance
- **Bacterial endocarditis** – inflammation and infection of the heart
- **Bleeding** – >5g/dl drop in hemoglobin or loss of blood requiring transfusion
- **Brachial plexus injury** – damage to brachial plexus
- **Bruising** – blood leakage under the skin at the groin, catheter access site
- **Cardiac arrest** – failure of the heart to contract
- **Cardiac perforation** – penetration of the heart wall
- **Cardiac tamponade** – constriction of the heart causing inefficient contraction resulting from accumulation of excess fluid in the pericardium
- **Congestive heart failure** – inability of the heart to keep up with its demands, specifically, failure of the heart to pump blood with normal efficiency
- **Death** – permanent cessation of all vital bodily functions
- **Delivery system failure** – the cable with the screw mechanism that the device is attached to when it is being placed in the heart does not work properly

- **Device embolization** – movement of device from its intended location
- **Device thrombus** – blood clot on the device
- **Device migration** – movement of device within the intended location
- **Dyspepsia** - indigestion
- **Erosion** - rubbing of device against myocardium or cardiac structure
- **Fever** – defined as body temperature greater than 101.5° F
- **Foreign body embolization** – movement of device material, delivery system material, or other material from its intended location
- **Gastrointestinal pain and/or bleeding** – pain or bleeding in the gastrointestinal tract
- **Hypotension** – sustained systolic BP < 40mmHg
- **Hypertension** – Systolic blood pressure of >160mmHg
- **Hypoventilation** – the state in which a reduced amount of air enters the in the lungs
- **Hemorrhagic Stroke** - acute focal neurological deficit presumed to be due to focal ischemia, with either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct with hemorrhagic conversion
- **Infection** – invasion and growth of a pathogenic organism within the body
- **Ischemic Stroke** – acute focal neurological deficit presumed to be due to focal ischemia, with either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct
- **Myocardial infarction (heart attack)** – the death of heart muscle from the sudden blockage of a coronary artery by a blood clot
- **Myocardial ischemia** – inadequate blood flow to the heart
- **Nickel sensitization**- alteration of the responsiveness of the body to nickel
- **Pericardial effusion** – abnormal fluid collection around heart without hemodynamic compromise
- **Peripheral thromboembolism** – blood clot in the peripheral vasculature
- **Perforation** – physical penetration of vessel or organ
- **Pleural Effusion** - abnormal fluid collection around the lungs
- **Renal failure** – inability of kidneys to perform normal functions
- **Respiratory failure** – inability of the lungs to perform normal functions
- **Respiratory insufficiency** – the condition in which the lungs cannot take in sufficient oxygen or expel sufficient carbon dioxide to meet the needs of the cells of the body
- **Seizure** – uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms
- **Sepsis** – the presence of bacteria or other infectious organisms or their toxins in the blood or in other tissue of the body

- **Septicemia** – systemic (body wide) illness with toxicity due to invasion of the bloodstream by virulent bacteria coming from a local seat of infection
- **Systemic Embolism** - an abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism
- **Thrombus** – a blood clot
- **Thrombophlebitis** - inflammation of a vein due to a blood clot
- **Tissue damage** - damage to cardiac tissue
- **Transient Ischemic Attack (TIA)** - acute focal neurological deficit (such as focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit) presumed due to focal ischemia, with symptoms persisting greater than or equal to 5 minutes and less than 24 hours, that is not associated with MR or CT findings of a new cerebral infarct
- **Valvular regurgitation / insufficiency** – backflow of blood during contraction of the heart; caused by a defective heart valve
- **Vascular dissection** - the process of cutting apart or separating vessel tissue
- **Vascular access site injury** – damage at vascular access site (e.g., AV fistula, hematoma, and aneurysm)

2.14 ADVERSE EVENT REPORTING

2.14.1 REPORTING ALL ADVERSE EVENTS

Investigators are responsible for promptly reporting all adverse events to AGA Medical by completing the Adverse Event CRF. All unresolved adverse events should be followed by the investigator until resolution; Adverse Event Follow-up CRF(s) must be completed.

2.14.2 REPORTING UNANTICIPATED ADVERSE DEVICE EFFECTS

An investigator shall submit to the Sponsor and the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than ten (10) working days after the investigator first learns of the effect (21 CFR 812.150 (a) (1)).

2.15 HYPOTHESIS AND STATISTICAL ANALYSIS

The ACP will be clinically evaluated for safety and effectiveness in subjects with nonvalvular atrial fibrillation who are at risk for ischemic strokes, and peripheral thromboembolism through a two arm, randomized, multi-center, controlled clinical trial. Subjects will be randomized to either the device arm or the control arm. The randomization ratio of device subjects to control subjects will be 2:1, that is, twice as many subjects will receive the device than receive warfarin therapy. The randomization will be stratified by study center, oral anticoagulant therapy (warfarin or dabigatran), and baseline concomitant aspirin usage. The ACP clinical trial will have two groups of subjects. The first 30 device subjects (plus any subjects with implant attempts) will constitute the feasibility group and all subjects (including the feasibility

group) will constitute the pivotal group. The primary safety and efficacy analysis will consist of all randomized subjects.

2.15.1 Feasibility Subset

The first 30 subjects who receive the ACP device (plus any subjects with device implant attempts), will compose the feasibility subset. The primary aim of this subset is to assess the incidence of serious adverse events (SAE) in the first 45 days after procedure. The 45-day SAE and TEE data for these first 30 device subjects will be submitted to the FDA. Enrollment will halt while the 30 day safety data are collected, analyzed, and submitted to FDA for review, although follow-up will continue among the device and control subjects already enrolled in the trial. The DSMB and/or CEC will also review this data prior to submission.

The date of the first attempted implant procedure will determine the subjects that qualify for this group. Since it may be difficult to determine which subject had the 30th ACP implant procedure, any subject with the same initial procedure date as another subject in this group will be reported among the feasibility group. This may increase the feasibility sample size beyond 30 subjects. In addition, subjects with an attempted, but not implanted device will be analyzed in this group but will not count towards the limit of 30; this may also increase the sample size beyond 30 subjects.

2.15.2 Pivotal Group

This group will consist of any subject in the study, randomized to either the device arm or the control arm (subjects treated with warfarin and dabigatran) in either the feasibility or pivotal group.

2.15.3 Study Design (REFER TO APPENDIX D)

The study is intended to determine the difference in efficacy and safety between the device arm and control arm (subjects treated with OMT).

The ACP clinical trial is an adaptive design with interim sample size analyses that use current data and project the necessary sample size and follow-up time based upon observed efficacy and safety event rates in the device and control subjects.

Three primary endpoints and hypotheses are being evaluated in the ACP clinical trial

1. An efficacy endpoint which compares the 2-year event rates of ischemic stroke and peripheral thromboembolism. This is a non-inferiority analysis where the device will be deemed efficacious if the risk ratio is < 1.75 or the risk difference in two years event rates is < 2.87.
2. A long-term safety endpoint which compares long-term composite rates of all-cause mortality and major bleed. This is a superiority analysis where the device will be deemed safe if the safety event rate in the device arm is proven superior to the safety event rate in the control arm (OMT).
3. An acute safety (short-term) endpoint which compares the rate of device or procedure related serious adverse events against a performance goal (PG). If this

rate is less than 5%, the device is considered to have met the acute safety endpoint.

The primary efficacy and primary long-term safety hypotheses are included in the adaptive design. The study will accrue subjects until there is high predictive probability that the sample size is sufficient to meet the efficacy and long term safety endpoints or until it is evident that in spite of enrolling to the maximum sample size it is unlikely to meet the efficacy and long-term safety endpoints.

The analysis for the primary acute safety endpoint will be performed on the entire sample size as determined by the adaptive design governed by the efficacy and long term safety endpoints.

The ACP clinical trial is powered to concurrently prove the non-inferiority efficacy endpoint, along with the acute and long-term safety endpoints. The precise follow-up time may vary in this adaptive design.
Interim sample size analyses will be performed when 400 subjects are enrolled, then again every 50 subjects until a possible maximum of 3000 subjects are obtained. Once subject accrual is stopped and the predictive probability of trial success for both efficacy and long-term safety is high, all subjects will be followed for at least 6 months. Additional analyses will be performed at 12, 18, and 24 months after accrual stops if the primary endpoints have not been met. For all subjects, assessment of primary endpoints begins at the time of randomization. Type I error is controlled for multiple sample size selection analyses and for multiple potential analyses at the end of accrual.

The statistical model is described in detail in subsequent sections. But at each interim analysis, two predictive probabilities are calculated:

a. The predictive probability of meeting the non-inferiority criteria for efficacy and the superiority criteria for long-term safety is calculated if subject accrual is stopped at the current sample size and enrolled subjects are continued to be followed for an additional two years. If this joint predictive probability exceeds the predictive success stopping boundaries, S_n, in **Table 1**, then accrual stops and enrolled subjects are continued to be followed. The first possible final analysis may be performed in 6 months with subsequent analyses possible at 12, 18, and 24 months after accrual ends.

Table 1: Cutoffs for stopping the trial forpredicted success, $S_{\underline{n}}$, or failure, $F_{\underline{n}}$.

Stopping Boundaries		
n	S_n	F_n
$400 \leq n < 500$	0.97	0.00
$500 \leq n < 600$	0.97	0.01
$600 \leq n < 700$	0.95	0.02
$700 \leq n < 800$	0.95	0.03
$800 \leq n < 900$	0.95	0.04
$900 \leq n < 1000$	0.95	0.05
$1000 \leq n < 3000$	0.90	0.05

b. The predictive probability of meeting the non inferiority criteria for efficacy and the superiority criteria for long-term safety is calculated if subject accrual is continued to the 3000 subject study maximum and then continue to follow all subjects for additional 2 years. If this predictive probability is less than the futility stopping bounds, Fn, in **Table 1**, then accrual ends and the trial stops for futility.

The total enrollment in the study will be a minimum of 400 and a maximum of 3000 subjects. Since the first interim analysis after the halting of subject accrual will be performed at six months, the minimum follow-up for any subject not lost to follow-up in the trial will be six months. The maximum length of follow-up will be the total duration of the trial plus at least 6 months (up to 2 years). Even if the trial stops for predicted success at the first interim analysis, with the expected accrual rate of 25 subject-per-month, the efficacy and safety are demonstrated at the first analysis at 6 months and 250 subjects would have 1 or more years of follow-up. This is the minimum possible exposure. As demonstrated in the operating characteristics (2.15.5), longer trials are expected.

2.15.3.1 Adaptive Design

The efficacy and long-term safety endpoints are modeled separately, but their combined probability of success is incorporated throughout the adaptive design. Statistical models for each are described separately in the following sections.

2.15.3.2 Primary Effectiveness Endpoint and Hypothesis

The primary effectiveness endpoint for the ACP study is the two-year annualized rate of ischemic stroke and peripheral thromboembolism. The rate will be calculated in each treatment arm using a piecewise exponential model (non-constant hazard rate) and assessing the number of primary endpoint events divided by the number of subject-years of follow-up within each timeframe. The 2-year event rate is then found by the product of not having an event during each segment. For subjects who have already experienced an endpoint, additional endpoints or follow-up time will not be factored into

this calculation. If a subject experiences a non-fatal safety event, he or she is still tracked for efficacy events.

Separate estimates will be performed for the posterior probability distributions for the two-year event rate in the subjects randomized to the device arm and for the two-year event rate for subjects randomized to the control arm. Once these estimates are obtained, the posterior probability distributions for both the risk ratio (device rate / control rate) and risk difference (device rate minus control rate) will be calculated.

Non-inferiority criterion will be considered met if either the hazard ratio of device to control rate is significantly less than 1.75, or if the risk difference is less than 2.87 percentage points.

Let π_{DEVICE} be the primary effectiveness endpoint rate in the device arm, while $\pi_{CONTROL}$ is the corresponding rate in the control arm. Specifically, the following null and alternative hypotheses will be tested:

$$H_0: \pi_{DEVICE} / \pi_{CONTROL} \geq 1.75$$
$$H_a: \pi_{DEVICE} / \pi_{CONTROL} < 1.75$$

where π_{DEVICE} equals the two-year event rate in the device arm and $\pi_{CONTROL}$ equals the two-year efficacy event rate in the control arm. The null hypothesis will be rejected and non-inferiority to OMT will be concluded if the upper bound of the two-sided 97.6% Bayesian confidence interval for the ratio between the device rate and control rate is less than 1.75. This is equivalent to testing whether the posterior probability, $Pr(\pi_{DEVICE} / \pi_{CONTROL} \geq 1.75) > 0.988$.

For the Risk Difference, the following hypotheses will be tested.

$$H_0: \pi_{DEVICE} - \pi_{CONTROL} \geq 2.87\%$$
$$H_a: \pi_{DEVICE} - \pi_{CONTROL} < 2.87\%$$

The null hypothesis will be rejected and non-inferiority to OMT will be concluded if the upper bound of the two-sided 97.6% Bayesian confidence interval for the difference between the two-year device rate and two-year control rate is less than 2.87%. This is equivalent to testing whether the posterior probability, $Pr(\pi_{DEVICE} / \pi_{CONTROL} \geq 1.75) > 0.988$.

97.6% confidence intervals are used so that the Type I error for the composite hypothesis test is not above a one-sided 2.5%.

With this combination of allowable risk ratio (1.75) and risk difference (2.87%) the Type I error rate is highest at $\pi_{CONTROL} = 3.82\%$ and $\pi_{DEVICE} = 6.69$ -- the point where π_{DEVICE} /

$\pi_{CONTROL}$ = 1.75 and π_{DEVICE} - $\pi_{CONTROL}$ = 2.87%. The type I error rate for this scenario is shown in **Table 5**.

If the device endpoint rate is shown to be successful for non-inferiority to control, it will then be tested for superiority. In that event, the following null and alternative hypotheses will be tested:

$$H_0: \pi_{DEVICE} - \pi_{CONTROL} \geq 0$$
$$H_a: \pi_{DEVICE} - \pi_{CONTROL} < 0$$

While the above hypotheses are stated as a subtraction of rates, it is equivalent to testing whether the ratio of the rates is lower than 1.0.

The following describes the Bayesian adaptive design for the primary efficacy endpoint. This design was created by Berry Consultants, (Austin, Texas) using the specific model assumptions for this trial.

The two-year event rates are calculated using a piecewise exponential model that recognizes that event rates may change during the course of subject follow-up.

The control arm uses a 7-piece model while the device arm uses an 8-piece model as described below:

Time intervals for the control arm:

- Day 0- Day 6
- Day 7- Day 30
- Day31- Day 60
- Day 61- 6 months
- 6 months-12 months
- 12 months -18 months
- 18 months-24 months

Time intervals for the device arm:

- Day 0 (randomization) to Day before Procedure Day (the procedure must occur by 14-days after randomization)
- Procedure Day to Procedure Day + 6 days
- Procedure Day + 7 days to Day 30
- Day 31- Day 60
- Day 61- 6 months
- 6 months -12 months
- 12 months-18 months
- 18 months-24 months

For tracking events and exposure, the last interval is open ended. This ensures all events observed are counted (e.g. an event that occurs at 2 years + 1 day will count toward the composite 2-year event rate by contributing to the 18-24 month interval).

The segments comprising the piecewise exponential are slightly different in the first 30 days between the two treatment arms. The benefit of this model is that it separately estimates:

- the risk from randomization to procedure (procedure day varies by subject, may range from 0 to 14),
- risk on the day of procedure and immediately afterward (a 7-day period for all subjects) and
- the risk in remainder of the first month (segment varies by subject, may range from 9 to 23 days)

The segments in the piecewise exponential are the same for the control and device arms after 30-days: 30-60 days, 61 days-6 months, then 6-month intervals thereafter.

The segments for the control arm (*G*=1) and device arm (*G*=2) are formally:

$$\lambda_{G=C}(t)=\begin{cases}\lambda_{C,1} & 1\le t<7\\ \lambda_{C,2} & 7\le t<30\\ \lambda_{C,3} & 30\le t<60\\ \lambda_{C,4} & 60\le t<182.5\\ \lambda_{C,5} & 182.5\le t<365\\ \lambda_{C,6} & 365\le t<547.5\\ \lambda_{C,7} & 547.5\le t<730\end{cases}$$

$$\lambda_{G=D}(t)=\begin{cases}\lambda_{D,0} & 0\le t<\text{ProcDay}\\ \lambda_{D,1} & \text{ProcDay}\le t<\text{ProcDay}+7\\ \lambda_{D,2} & \text{ProcDay}+7\le t<30\\ \lambda_{D,3} & 30\le t<60\\ \lambda_{D,4} & 60\le t<182.5\\ \lambda_{D,5} & 182.5\le t<365\\ \lambda_{D,6} & 365\le t<547.5\\ \lambda_{D,7} & 547.5\le t<730\end{cases}$$

For estimating the two-year event rates the exponential distribution and the at-risk time in each period is used. For estimating the two-year event rates in the device arm, it is assumed that the procedure takes place on day 10 following randomization.

$$\pi_C = \Pr(\text{Event by 2 years in Control Group})$$
$$= 1 - \exp\left(-\left(6\lambda_{C,1} + 24\lambda_{C,2} + 30\lambda_{C,3} + 122.5\lambda_{C,4} + 182.5\lambda_{C,5} + 182.5\lambda_{C,6} + 182.5\lambda_{C,7}\right)\right)$$

$$\pi_D = \Pr(\text{Event by 2 years in ACP Device Group})$$
$$= 1 - \exp\left(-\left(10\lambda_{D,0} + 7\lambda_{D,1} + 13\lambda_{D,2} + 30\lambda_{D,3} + 122.5\lambda_{D,4} + 182.5\lambda_{D,5} + 182.5\lambda_{D,6} + 182.5\lambda_{D,7}\right)\right)$$

A sensitivity analysis will also calculate the posterior distributions for 2-year event rates based upon the observed average day of procedure and compare it to the *a priori* assumption of Day 10 (assuming it takes on an average 10 days for procedure to occur). The fixed value of day 10 is important for the algorithm used at each interim analysis of the adaptive design.

Each piecewise event rate estimate uses a vague prior distribution in both the device and control arms.

$$\lambda_{G,j} \sim \Gamma(a = 0.0000438, b = 1.0)$$

Where *G=D* or *C* for the event or device arm, respectively. Upon observing EV_j events during EXP_j subject-days of follow-up in group j, the posterior distribution becomes:

$$\lambda_{G,j} \mid EV_{G,j}, EXP_{G,j} \sim \Gamma(a + EV_{G,j}, b + EXP_{G,j})$$

The model is parameterized in terms of subject-days. This prior has mean 0.016 events per subject-year (365 × a ÷ b = 0.016) and has the equivalent of just one subject-day of follow-up. Therefore the prior is rapidly overcome by the accumulating data.

Once posterior distributions are obtained for each segment, one can calculate the posterior distribution for each two-year event rate, and then calculate the posterior distribution for π_D/π_C and $\pi_D - \pi_C$. If $\Pr(\pi_D/\pi_C \leq 1.75 \mid EV_C, EXP_C, EV_D, EXP_D) > 0.988$ or $\Pr(\pi_D - \pi_C \leq 0.0287 \mid EV_C, EXP_C, EV_D, EXP_D) > 0.988$, then the null hypothesis will be rejected and the trial will conclude that the relative risk is less than 1.75 and/or risk difference is less than 2.87%.

As long as the trial does not stop for futility, up to four predefined analyses will be performed. The first analysis will occur 6 months after the final subject is randomized. If non-inferiority for efficacy and superiority for safety are not declared, subsequent analyses will be performed every 6 months with the final analysis 24 months after the final subject is enrolled and randomized. A 98.8% posterior probability will be used, this is equivalent to a two-sided equitailed 97.6% CI. This is to conserve Type I error at 2.5% -- Type I error can be inflated in three ways in the efficacy part of the trial: because the risk ratio or risk difference may be used to demonstrate non-inferiority, because multiple same size looks are made, and because 4 possible final analysis between 6 and 24 may be conducted.

The trial will stop in one of three circumstances: (a) the trial stops early for futility, (b) the non-inferiority definition is not met by any of the 4 analysis -6, 12, 18, or 24 months after the final subject is randomized, (c) the non-inferiority definition is met in one of the four analyses described above. Only circumstance (c) results in an efficacy success.

2.15.3.3 Primary Effectiveness Endpoint Interim Analyses

The interim sample size analyses within the adaptive design will be used to determine sample size. At each interim analysis predictive probabilities of trial success are calculated based upon the current sample size and enrolling to the maximum sample size.

Once 400 subjects are enrolled, then again for every 50 subjects up to a maximum of 3000, an analysis will be performed that could stop the study for futility, or stop accrual if there is a sufficient predictive probability of showing success. The interim analyses are used solely to select a sample size. If accrual ends for predicted success, then the final analyses are conducted as described in the previous section starting six months later.

At each interim analysis, observe the number of composite events, $EV_{G,j}$, and subject-years of follow up, $EXP_{G,j}$, in interval j, for group G = C (control) or D (device) for each segment. Using the informative prior

$$\lambda_{G,j} \sim \Gamma(a = 0.5, b = 11406.25)$$

the current posterior probability distribution for each event rate is calculated

$$\lambda_{G,j} \mid EV_{G,j}, EXP_{G,j} \sim \Gamma(a = 0.5 + EV_{G,j}, b = 11406.25 + EXP_{G,j})$$

The mildly informative prior has the equivalent of one-half a subject's worth of information with a mean of 0.016 events per subject year within each segment ($365 \times 0.5 \div 11406.25 = 0.016$ events per subject-year). These priors are used only to help select the sample size – they are not used for the final analysis. Again the prior is in patient-days of exposure, but we transform these to 2-year event rates in the analysis.

Subjects who have experienced an endpoint event provide complete data. Subjects who have not experienced an event inform the posterior distribution through their exposure time. But whether and when such a subject will experience an event remains uncertain, and therefore it has a probability distribution. Based on the posterior distributions of the $\lambda_{G,j}$ at each analysis one can find the predictive distributions of the number of events (and their timing) for all subjects currently in the trial (by treatment arm) if they continue to be tracked.

This probability is calculated by first sampling each $\lambda_{G,j}$ from their respective posterior distribution and using a sect of logical statements constructing if and when each subject would experience an event within the remaining trial duration. Then each simulation for each 'completed trial' can total the number of observed events, EV^*_G (EV_G will have been truly observed and the rest imputed) and total exposure EXP^*_G. Then using this set of piecewise exponentials, the posterior distribution for the 2-year event rate π_G, is calculated for each group. This is used to track whether $Pr(\pi_D/\pi_C < 1.75) > 0.988$ and/or $Pr(\pi_D - \pi_C < 2.87\%) > 0.988$. This process is repeated 1000 times which has the effect of integrating over the uncertainty present in the current distribution of π_i . The proportion of simulations in which $Pr(\pi_D/\pi_C < 1.75) > 0.988$ and/or $Pr(\pi_D - \pi_C < 2.87\%) > 0.988$ is the predictive probability of demonstrating non-inferiority for efficacy.

Because there may be little long-term follow-up at the early interim analyses it is assumed that $\lambda_{C,5}=\lambda_{C,6}=\lambda_{C,7}$ and $\lambda_{D,5}=\lambda_{D,6}=\lambda_{D,7}$ in the interim analyses. Again this assumption is only used during the interim analyses to select sample size. The final analysis uses the model where each segment has its own distribution.

2.15.3.4 Primary Safety Endpoints and Hypotheses

The **primary safety endpoint** for the ACP study has two components: acute safety and long-term safety.

a. Acute safety consists of procedure related serious adverse events that qualify as one of the following:

- procedure-related death (i.e., death occurring during the implantation procedure).
- pericardial effusion requiring treatment.
- device embolization.
- access site-related bleeding requiring transfusion ≥ 2 units.
- damage to other cardiac or major non-cardiac cardiovascular structures

The acute analysis does not inform the adaptive design in that its probability of success does not affect the adaptive sample size algorithm.

In the acute safety analysis, the rate of device or procedure related serious adverse events from the time of randomization until hospital discharge is compared against a performance goal (PG) of 5.0% chosen from the literature.

Let π_{DEVICE} be this pre-discharge event rate in the device arm. Specifically, the following null and alternative hypotheses will be tested:

H_0: $\pi_{DEVICE} \geq$ (PG = 5.0%)
H_a: $\pi_{DEVICE} <$ (PG = 5.0%)

The null hypothesis will be rejected and the performance goal will be considered met if the upper bound of the one-sided confidence interval for the device rate is less than 5.0%.

b. Long-term safety events can occur in either the device arm or the control arm and consist of the following:

1. All-cause death; or
2. Major bleeding defined as:
   a. Symptomatic intracerebral or intraventricular hemorrhage; or subdural, subarachnoid, epidural, or ocular hemorrhage; or
   b. Major non-cerebral bleed-defined as transfusion requiring ≥ 2units, hospitalization requiring any transfusion or surgical or percutaneous interventional procedure to treat bleeding

Note: procedure-related pericardial effusions requiring treatment will not be counted as a major non-cerebral bleed

Subjects who experience a non-fatal efficacy event are still followed and included in the safety analysis.

The long-term safety analysis is a two-arm analysis that compares the safety events defined above between the device and the control arm. For both the device arm and the control arm, the events will be evaluated from the time of randomization until two years. This analysis will test for superiority of the device arm versus the control arm.

Let γ_{DEVICE} be the long-term safety endpoint rate in the device arm, while $\gamma_{CONTROL}$ is the corresponding rate in the control arm. Specifically, the following null and alternative hypotheses will be tested:

H_0: $\gamma_{DEVICE} / \gamma_{CONTROL} \geq 1.0$
H_a: $\gamma_{DEVICE} / \gamma_{CONTROL} < 1.0$

The null hypothesis will be rejected and superiority to warfarin therapy will be concluded if the upper bound of the two-sided 98.4% confidence interval for the ratio between the device rate and control rate is less than 1.0.

To test this, the number of events, EVS_G and amount of exposure $EXPS_G$ are tracked within each group. Vague gamma priors are employed for the safety event rates in each group G=C for control or D for device.

$$\gamma_G \sim \Gamma(0.0002356, 1)$$

that have mean 0.086 events per subject-year (365 × a ÷ b = 0.086) with the equivalent of one subject-day of follow-up. The posterior distributions become

$$\gamma_G \mid EVS_G, EXPS_G \sim \Gamma(0.0002356 + EVS_G + , 1 + EXPS_G)$$

Each final analysis calculates the posteriors for the device (G=D) and control (G=C) groups and the posterior distribution for the risk ratio γ_D / γ_C. If the equitailed 98.4% confidence interval is less than 1.0, then the long-term safety rate is proven superior to control. This is the equivalent of $Pr(\gamma_D / \gamma_C < 1.0) > 0.992$.

2.15.3.5 Long-term Safety Interim Analyses

Similar to the primary efficacy endpoint, an interim analysis is performed to determine the long-term safety. This analysis will be performed after 400 subjects are enrolled and will occur at every 50 subjects enrolled up to a maximum of 3000 to calculate the predictive probability.

At each interim analysis, observe the number of long-term safety events, $EVS_{\underline{G}}$, and subject-years of follow up, $EXPS_{\underline{G}}$, in each group G = C (control) or D (device) for each segment. Using the informative prior

$$\gamma_G \sim \Gamma(a = 0.5, b = 2122.093)$$

the current posterior probability distribution for each event rate is calculated

$$\gamma_G \mid EVS_G, EXP_G \sim \Gamma(a = 0.5 + EVS_G, b = 2122.093 + EXPS_G)$$

The mildly informative prior has the equivalent of one-half a subjects worth of information with a mean of 0.086 events per subject year (365 × 0.5 ÷ 2122.093=0.086 events per subject-year). These priors assist in selecting the sample size and are not used for the final analysis.

Subjects who have experienced a long-term safety endpoint event provide complete data. Subjects who have not experienced such event inform the posterior distribution through their exposure time. But whether and when such a subject will experience an event remains uncertain, and therefore it has a probability distribution. Based on the posterior distributions of the $\gamma_{\underline{G}}$ at each analysis the predictive distributions of the number of safety events (and their timing) can be determined. This determination can be made for all subjects currently in the trial (by treatment arm) if they continue to be tracked.

This probability is calculated by first sampling $\gamma_{\underline{G}}$ from its respective posterior distribution at the current interim analysis, then times to safety events are

generated for all subjects remaining at risk at the interim analysis (these events may be censored as time left in trial is accounted for). Using this full dataset imagining the subjects are tracked for an additional time period, one can calculate the total number of events EVS^*_G and exposure time $EXPS^*_G$ in each group. Once this is obtained, a final analysis is performed using the methods described in the previous section and calculate the $Pr(\gamma_D/\gamma_C < 1.0)$. If this value is greater than 0.992 it predicts a win on the long-term safety endpoint. Repeating this process 1000 times at each interim analysis estimates the predictive probability of demonstrating long-term safety superiority.

2.15.3.6 Predictive Probability Calculations

The predictive probabilities of meeting the non-inferiority efficacy goal and superiority safety goal are calculated at each interim analysis as described in sections 2.15.3.3 and 2.15.3.5. Likewise the joint predictive probability of achieving the efficacy and safety goals are calculated assuming accrual stops at the current sample size and if it continues to the maximum sample size.

$P_{\underline{n,n}}$ is the predictive probability of demonstrating non-inferiority (via the risk ratio OR the risk difference) for efficacy AND superiority for long-term safety if the study stops accruing subjects and wait for 24 months to perform the final analysis.

By continuing to enroll from the current sample size *n* subjects to the 3000 subject maximum, and then tracking all subjects another 2-years, , the predictive probability $P_{\underline{n,3000}}$ of demonstrating non-inferiority (via the risk ratio OR the risk difference) for efficacy AND superiority for long-term safety can be calculated.

If $P_{\underline{n,n}}$ is large, then there is a high probability that stopping accrual and following subjects for an additional two years will result in a final analysis that demonstrates sufficient efficacy and long-term safety. If $P_{\underline{n,n}} \geq S_{\underline{n}}$ (as shown in **Table 1**) then the DSMB and/or CEC is informed that the algorithm indicates that accrual should stop.

If $P_{\underline{n,3000}} < F_{\underline{n}}$, then there is a small chance of trial success even if the study runs to its maximum sample size and again the DSMB/CEC will be informed that the algorithm indicates that the trial should stop for futility. The subjects will be informed of this circumstance and enrollment will end. Enrolled subjects will be followed for a total of additional two years.

If $F_{\underline{n}} \leq P_{\underline{n,3000}}$ and $P_{\underline{n,n}} > S_{\underline{n}}$, the enrolling of subjects continues. Another sample size re-estimation will be performed once another 50 subjects are enrolled. Sample size analyses continue every 50 subjects until $P_{\underline{n,n}} \geq S_{\underline{n}}$, or $P_{\underline{n,3000}} < F_{\underline{n}}$, or the maximum number of subjects,3000, is reached.

If $P_{\underline{n},n} > S_{\underline{n}}$ or the maximum number of subjects is obtained, analyses will be performed every 6 months as described in the previous section up to 24 months after the date the last patient is enrolled.

2.15.4 Analysis of Secondary Endpoints (REFER TO APPENDIX D)

Three comparisons for secondary endpoints will be made between the OMT control group and the device group at the end of the trial. The secondary endpoints of rate of TIA and asymptomatic intracerebral or intraventricular hemorrhage will be considered for labeling. Therefore a Type I error rate of 0.05/2 =.025 for each of these two endpoint analysis will be used.

- **Rate of Transient Ischemic Attacks -** The rate of TIAs will be compared between the device arm and control arm and tested for significance. The null and alternative hypotheses for this comparison are given below:

$$H_0: \tau_{DEVICE} = \tau_{CONTROL}$$
$$H_A: \tau_{DEVICE} \neq \tau_{CONTROL}$$

where τ_{DEVICE} is the rate of TIAs in the device arm per 100 subject years, while $\tau_{CONTROL}$ is the corresponding rate in the control arm. The test will be a two sided test with a Type I error of 0.025. However superiority will only be claimed if the observed rate of TIAs in the device arm is less than the control rate. The TIA events are expected to be Poisson distributed. However, unlike the primary effectiveness endpoint it will be tested for superiority rather than non-inferiority.

The expected rate of TIAs in the control arm is expected to be 1.1 events per 100 subject years. This estimate is made from combining results found in meta-analyses by Aguilar (2008) and Reynolds (2004). The expected rate in the device arm is not known, but expected to be lower since TIAs are correlated with stroke.

- **Asymptomatic intracerebral or intraventricular hemorrhage** - The rate of asymptomatic intracerebral or intraventricular hemorrhage will be summarized for differences between the device and control arms

$$H_0: \phi_{DEVICE} = \phi_{CONTROL}$$
$$H_A: \phi_{DEVICE} \neq \phi_{CONTROL}$$

where ϕ_{DEVICE} is the rate of hemorrhage in the device arm per 100 subject years, while $\phi_{CONTROL}$ is the corresponding rate in the control arm. The test will be a two sided test with a Type I error of 0.025. However superiority will only be claimed if the observed rate of hemorrhage in the device arm is less than the control rate. The hemorrhage events are expected to be Poisson distributed. However, unlike the primary effectiveness endpoint it will be tested for superiority rather than non-inferiority.

- **Atrial fibrillation status** - The rate of atrial fibrillation status, defined as subjects who progress from paroxysmal to persistent AF, or subjects who progress from persistent to permanent AF, will be summarized for differences between the device and control arms. The rates for each group will be summarized, and the difference between the two expressed as an estimate with a corresponding two sided 95% confidence interval. This endpoint will not be considered for labeling purposes.

While the above endpoints will compare the two treatment arms, the following endpoints will only be assessed in the device arm. They will be summarized as estimated rates with corresponding two sided 95% confidence intervals. No formal hypotheses will be performed for these tests.

- **Device or Procedure Related Adverse Events -** The rate of the following device or procedure related adverse event components will be summarized. However confidence intervals will only be summarized for the composite rate, that is, for the percentage of subjects who experience any one of these events.

    - Device embolization
    - Myocardial perforation (hemopericardium) or any pericardial effusion requiring drainage
    - Endocarditis
    - Thrombus on device

- **In-hospital procedure success:** Successful implantation of the ACP with no in-hospital serious adverse events in subjects randomized to the treatment arm

- **"Day 45" clinical success:** In-hospital procedure success, closure of LAA documented at Day 45 TEE, no ischemic stroke or peripheral thromboembolism, and discontinuation of warfarin or dabigatran

- **Long-term clinical success:** In-hospital procedure success, closure of LAA documented at Day 45 TEE, no ischemic stroke or peripheral thromboembolism, and sustained discontinuation of warfarin or dabigatran (without temporary re-administration of warfarin or dabigatran) at last available follow-up. Subjects who continue or restart warfarin or dabigatran due to medical necessity (e.g. for DVT treatment) rather than LAA closure status will not be considered device failures for the purpose of this analysis.

- **Technical Success and Complete Closure** - The secondary endpoints of technical success, and complete closure will only be evaluated in the device arm and will each be summarized as a point estimate with a corresponding

99.5% confidence interval. However, no formal hypotheses will be tested for these endpoints.

2.15.5 Derivation of the operating characteristics for both device and control arms

2.15.5.1 Primary Effectiveness

2.15.5.1.1 Primary Effectiveness - Control

The Bayesian simulation models for the current study design require two-year rate estimates for effectiveness analysis and one-year rates for safety.

The two-year rate for the control effectiveness endpoint of ischemic stroke, and peripheral thromboembolism was derived from a literature review. There were three primary sources (**Table 2**) used for determining this rate.

The first source was the pivotal study report of dabigatran published by Connolly et al (NEJM 2009). This study compared the primary outcome of stroke and systemic embolization in subjects randomized between warfarin and either 110 mg or 150 mg of dabigatran. Connolly, 2009 reported the following endpoints among 12,098 subjects (randomized to warfarin or 150mg dabigatran).

Primary Efficacy – (n=6022 warfarin) = 2.55% (two years)
Primary Efficacy – (n=6076 dabigatran) = 2.12% (two years)

The second source was the ARISTOTLE trial (Granger et al, NEJM 2011), which reported the following endpoint component rates among 9081 control subjects (randomized to warfarin).

Primary Efficacy – (n=9081 warfarin) = 2.27% (two years)

The third source was the ROCKET AF trial (Patel et al, NEJM 2011), which reported the following endpoint component rates among 7133 control subjects (randomized to warfarin).

Primary Efficacy – (n=7133 warfarin) = 3.81% (two years)

Table 2. Derivation of primary long term efficacy control rates for ACP$^{\phi}$

Trial/ Arm	Smple Size	Mean CHADS(2)	Primary endpoint* rate (%)	Ischemic. (or unknown) Rate(%)	Hemorrhagic stroke Rate(%)	Systemic Embolization Rate(%)	Ischemic. (or unknown) + Systemic Embolization(%)	Study Weight
RE-LY Dabigatran	6076	2.2	1.11	0.92	0.10	0.15	**1.07**	**50%**
RE-LY Warfarin	6022	2.1	1.69	1.20	0.38	0.09	**1.29**	**10% weighted by sample size**
ARISTOTLE Warfarin	9081	2.1	1.60	1.05	0.47	0.10	**1.15**	
ROCKET-AF Warfarin	7090	3.46	2.42	1.72$^{\Psi}$	0.48$^{\Psi}$	0.22$^{\Psi}$	**1.94**	**40%**

*Composite endpoint of stroke and/or systemic embolism. Stroke defined as ischemic, hemorrhagic, or of uncertain type.

$^{\Psi}$In the ROCKET AF trial, primary efficacy endpoints in the Intent-to-treat cohort were reported only in a composite form. "Safety Population" effectiveness data reported in document #EDMS-ERI-24510755:2.0 Advisory Committee Briefing Document was used to determine the proportion of the overall rate represented by each type of event (ischemic/unknown stroke = 71%; hemorrhagic stroke=20%; and systemic embolization = 9%). These proportions were applied to the "Intent-to-treat population" overall rate (2.42%) to estimate the rate of each component.

$^{\phi}$Rates listed in table 2 are one year rates

The two-year weighted average of these three trials (assuming a 50% adoption rate of dabigatran) is 2.95%[1] endpoint events.

2.15.5.1.2 Primary Effectiveness - Device

The two-year rate for the device effectiveness pivotal endpoint of ischemic stroke and peripheral thromboembolism was derived from published experience to-date with the ACP device. There were two primary sources used for determining this rate.

The first source was the 30 subjects from the feasibility phase that were randomized and received a device

- Ischemic stroke – 1.0 event (six months)
- Peripheral thromboembolism – 0.0 events (six months)

In this phase, one event out of 30 (1/30, 3.3%) occurred over six months of follow up.

[1] Two-year rates calculated using the following formula for change over time (=1-exp(2*0.016))

The second source was derived from subjects enrolled in the ACP Registry (ACPR) (Park et al), which reported the following endpoint component rates among 197 subjects.

- Ischemic stroke – 2.0 events (six months)
- Peripheral thromboembolism – 0.0 (six months)

The calculated rate in the ACPR is (2/197) 1.0%.

The weighted average of these two trials is 1.32% endpoint events per six months. To estimate a two-year rate from these six-month endpoints, Kaplan-Meier curves were analyzed from the PROTECT AF study (SSED). This analysis showed an increase of 124% from six months to two years for the primary effectiveness endpoint. Employing this percent change over time corresponds to an estimated two-year rate of 2.96%. For non-inferiority assumptions 2.95% will be used to match the control primary effectiveness estimated rate from above.

2.15.5.2 Primary Safety

2.15.5.2.1 Procedural (Acute) Safety- This analysis compares the rate of procedure related serious adverse events (SAE) as listed below, that occur in the device arm from the time of randomization until hospital discharge to a performance goal (PG) chosen from the literature. The endpoint will be considered met if the 96% credible interval for the in-hospital event rate is entirely less than the PG.

- procedure-related death (i.e., death occurring during the implantation procedure).
- pericardial effusion requiring treatment.
- device embolization.
- access site-related bleeding requiring transfusion ≥ 2 units.
- damage to other cardiac or major non-cardiac cardiovascular structures

A literature search was conducted in order to establish a PG. The search criteria included catheter ablation for atrial fibrillation. This criterion was chosen because catheter ablation utilizes transseptal puncture to access the left atrium which is the common technique used to access the left atrial appendage and implant the ACP device. The search included electrophysiologic (EP) studies and summaries of safety and effectiveness (SSED).

In all, 29 sources (27 published articles and two SSEDs) were examined for reported complications of procedure related SAE (as listed above). Serious Adverse Events of procedure-related death (i.e., death occurring

during the implantation procedure), access site-related bleeding requiring transfusion ≥ 2 units and device embolization was clearly reported. The Atritech SSED served to provide an estimate of the rate for device embolization since the EP literature would lack this complication. However, in order to categorize literature reported complication against 'pericardial effusion requiring treatment' and 'Damage to other cardiac or major non-cardiac cardiovascular structures' the following criteria were used:

- Pericardial effusion requiring treatment included pericardial effusions that required pericardiocentesis and cardiac tamponade. Also included within this category are pericardial effusions that were medically treated, or where treatment was not specified. Please note this category does not include effusions that were spontaneously resolved.
- Damage to other cardiac or major non-cardiac cardiovascular structures included serious complications requiring more than conservative medical attention such as pleural effusion, pneumo- or hemothorax, lung injury , pulmonary edema, valve damage, vascular injury including arteriovenous fistulae requiring surgical intervention, aortic dissection, ,aortic root puncture and coronary sinus perforation.

The average weighted complication rate derived from literature Meta-analysis is provided in **Table 3.**

Table 3- Performance Goal

Death (procedure-related)	Device Embolization	Access Site Bleeding (requiring ≥ 2 units)	Damage to Other Cardiac or Major Non-Cardiac Cardiovascular Structures	Pericardial Effusion (requiring treatment)
0.05%	0.22 %	2.97%	0.46%	1.23%
Average Weighted Complication Rate= 4.93%				

Therefore a performance goal of 5% is being established, against which the acute safety profile of the ACP device will be compared. A performance goal of 5% provides confidence that it adequately represents a threshold between event rates observed in literature and is clinically relevant. The ACP trial will meet its acute safety success if the two-sided 95% credible interval lies entirely below this PG.

2.15.5.3 Long-Term Safety

2.15.5.3.1 Long-term Safety – Control

The one-year rate for the control safety endpoint of major bleeds and all-cause mortality was derived from the same literature review as cited

above (Connolly 2009, Granger 2011, Patel 2011) for effectiveness endpoint determination.
In sum:
Safety event rates from the OAC literature listed the following one-year event rates:

- RE-LY treatment arm (N=6076, dabigatran) = 6.75%
- RE-LY control arm (N=6022, warfarin) = 7.49%
- ARISTOTLE control arm (N=9081, warfarin) = 7.03%
- ROCKET AF control arm (N=7133, warfarin) = 8.37%

The weighted average of these three trials is 7.17% (assuming a 50% adoption rate of dabigatran) endpoint events per year.

The distribution of dabigatran and warfarin use will be monitored during the course of the trial. If a significant deviation from the expected adoption rate is observed, its potential impact will be assessed and appropriate adjustments to base rates and sample size calculations may be re-visited and/or re-modeled as appropriate.

2.15.5.3.2 Long-term Safety – Device

The one-year rate for the device safety pivotal endpoint of major bleeds and all-cause mortality was also derived from published experience to-date with the ACP device.

- Safety endpoints from the feasibility phase were:
  1/30 (3.3%) (six months)

- Safety endpoints from the ACP Registry (ACPR) were:
  10/197 (5.1%) (six months)

The weighted average of these two trials is 4.85% endpoint events per six months. To estimate a one-year rate from these six-month endpoints, Kaplan-Meier curves were analyzed from the PROTECT AF study (SSED). This analysis showed an increase of 6.2% from six months to one year for the primary safety endpoint. Employing this percent change over time corresponds to a one-year rate of 5.15%, the primary rate used for the calculations of the device safety endpoint.

2.15.5.3.3 Operating Characteristics, Power, and Type I Error

For the Bayesian adaptive design the power will be calculated using simulations. Besides design features described above, three other factors contribute to the study's power: the true unknown event rate, the unknown accrual rate, and the lost-to-follow-up rate observed in study subjects. The accrual rate can be controlled to some extent by the number of sites and

inclusion criteria, and the event rate can be projected based on the study's inclusion criteria.

To find operating characteristics, 1000 trials are simulated from each of 10 different scenarios. To simulate trials the following assumptions are made about the data-generating process. These are necessary to estimate operating characteristics but will not be used in the analysis of the actual trial.

- Times to efficacy events have an exponential distribution within each time period in both the device and control arms with the specified rate
- Times to safety events have an exponential distribution in both the device and control arms with the specified event rate
- There is 5% yearly lost-to-follow-up.
- Accrual is constant 25 subjects per month. (While accrual is not expected to be constant during the ACP trial, it is expected to be lower earlier and then stabilize after all sites have begun enrollment. If this is the case, then early subjects will have greater follow-up and the power calculations below will be underestimates.)

Operating characteristics have been calculated for a variety of accrual rates, efficacy event rates and safety event rates.

Tables 4a and **4b** illustrate the 10 scenarios used. Each row shows one parameter used to generate trial data used in the simulations.

Scenarios 1-4 in **Table 4a** represent Scenarios in the null space where Type I error should be 2.5% or less. Scenario 1 is when the device is neither non-inferior for efficacy nor superior for safety. Scenario 2 fails to meet the definition for efficacy non-inferiority, Scenario 3 fails to meet the definition for superiority for safety. The efficacy scenarios are shown where Type I error should be the highest. Scenario 4 shows the Type I error rate for the expected control event rate for efficacy. The six scenarios in **Table 4b** illustrate cases where the ACP device is non-inferior for efficacy and superior for safety.

Table 4a. Scenarios for 4 NULL cases where non-inferior efficacy and/or superiority safety case is not met.

Scenario	1	2	3	4
$\lambda_{C,1}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{C,2}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{C,3}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{C,4}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{C,5}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{C,6}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{C,7}$	0.019497	0.019497	0.014972	0.019497
$\lambda_{D,0}$	0.034635	0.034635	0.014972	0.034635
$\lambda_{D,1}$	0.034635	0.77	0.77	0.77
$\lambda_{D,2}$	0.034635	0.0274	0.00756	0.0274
$\lambda_{D,3}$	0.034635	0.0274	0.00756	0.0274
$\lambda_{D,4}$	0.034635	0.0274	0.00756	0.0274
$\lambda_{D,5}$	0.034635	0.0274	0.00756	0.0274
$\lambda_{D,6}$	0.034635	0.0274	0.00756	0.0274
$\lambda_{D,7}$	0.034635	0.0274	0.00756	0.0274
π_C	3.82%	3.82%	2.95%	3.82%
π_D	6.69%	6.69%	2.95%	6.69%
$\pi_D - \pi_C$	2.87%	2.87%	0.00%	2.87%
π_D / π_C	1.75	1.75	1.0000	1.75
γ_C	0.0717	0.0717	0.0717	0.0717
γ_D	0.0717	0.0717	0.0717	0.0515
γ_D / γ_C	1	1	1	0.718
Efficacy	NULL	NULL	Non-inf	NULL
Safety	NULL	NULL	NULL	Superior

Table 4b. Scenarios for 6 cases where non-inferior efficacy and superiority safety case are met.

Scenario	5	6	7	8	9	10
$\lambda_{C,1}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{C,2}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{C,3}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{C,4}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{C,5}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{C,6}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{C,7}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{D,0}$	0.01497	0.01497	0.01497	0.01497	0.00749	0.02246
$\lambda_{D,1}$	0.77	0.01497	0.4	0.114	0.385	1.155
$\lambda_{D,2}$	0.00756	0.01497	0.068	0.114	0.00378	0.01134
$\lambda_{D,3}$	0.00756	0.01497	0.068	0.114	0.00378	0.01134
$\lambda_{D,4}$	0.00756	0.01497	0.00756	0.00756	0.00378	0.01134
$\lambda_{D,5}$	0.00756	0.01497	0.00756	0.00756	0.00378	0.01134
$\lambda_{D,6}$	0.00756	0.01497	0.00756	0.00756	0.00378	0.01134
$\lambda_{D,7}$	0.00756	0.01497	0.00756	0.00756	0.00378	0.01134
π_C	2.95%	2.95%	2.95%	2.95%	1.49%	4.39%
π_D	2.95%	2.95%	2.95%	2.95%	1.49%	4.39%
$\pi_D - \pi_C$	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
π_D / π_C	1.00	1.00	1.00	1.00	1.00	1.00
γ_C	0.0717	0.0717	0.0717	0.0717	0.0717	0.0717
γ_D	0.0515	0.0515	0.0515	0.0515	0.0515	0.0515
γ_D / γ_C	0.7183	0.7183	0.7183	0.7183	0.7183	0.7183
Efficacy	Non-inf	Non-inf	Non-inf	Non-inf	Non-inf	Non-inf
Safety	Superior	Superior	Superior	Superior	Superior	Superior

Table 5 summarized the operating characteristics for each scenario. Each two rows show one scenario. The columns reflect the summary statistics for the 1000 simulations per scenario:

Mean N	Mean sample size
SD N	Standard deviation of sample size
Stop Early	Proportion of trials that stop early for predicted success
Stop Max	Proportion of trials that accrue to maximum 3000 subjects
Stop Futility	Proportion of trials that stop early for futility
Efficacy Power	Proportion of trials that meet either definition of non-inferiority efficacy success
Ratio	Proportion of trials with $Pr(\pi_D/\pi_c < 1.75) \geq 0.988$
Diff	Proportion of trials with $Pr(\pi_D - \pi_c < 2.87\%) \geq 0.988$
Safety Power	Proportion of trials that meet safety definition of superiority success, $Pr(\gamma_D / \gamma_C < 1.0) \geq 0.992$.
Power	Proportion of trials meeting both efficacy and safety goals.
N 0-1	Mean number of patients with less than 1 year of follow-up in successful trials (trials meeting efficacy and safety endpoints)
N 1-2	Mean number of patients with 1-2 years of follow-up in successful trials (trials meeting efficacy and safety endpoints)
N 2+	Mean number of patients with greater than 2 years of follow-up in successful trials (trials meeting efficacy and safety endpoints)

The second line in each scenario shows the same success probabilities if the analysis is repeated using an as-treated analysis that censors subjects randomized to the device who crossover and use warfarin 45 days or more after their procedure. Simulations verify that adequate power is maintained to interpret the primary effectiveness endpoint. For a detailed calculation please refer to the second line (AT = As Treated) under each scenario in **Table 5**. Here we assume 9% of subjects crossover immediately, 12.5% are censored at 45-days, then 5% are censored per year.

Scenarios 1-4 and show that Type I errors rate are all $\leq$2.5% (in bold). In these situations trials stop early for futility 88 – 100% of the time. The same "Power" column shows powers for the safe and efficacious scenarios. For example Scenario 5, the expected scenario, has 91% power. For other safe (superior) and efficacious (non-inferior) scenarios the trial offers ≥89% power.

In this expected scenario (5) the average sample size is 1880 subjects and the trial stops early for predicted success 88% of the time. The average trial size in the null cases is 906-1919.

While the trial's sample size may range from 400 to 3000 subjects, the average trial size, which varies by scenario, ranges from 906 to 2350 subjects for the scenarios shown here.

Scenarios 5-9 illustrate safe and efficacious cases. In these scenarios, the average number of patients with two or more years of follow-up ranges from 1303-1816 patients.

Table 5- Operating Characteristics for Bayesian Adaptive Design

Scenario	Mean N	SD N	Stop Early	Stop Max	Stop Futility	Efficacy Power	Ratio	Diff	Safety Win	Power	N 0-1	N 1-2	N 2+	Analysis
1	906	396	0.000	0.000	1.000	0.000	0.000	0.000	0.000	**0.000**	--	---	---	ITT
						0.000	0.000	0.000	0.000	0.000	--	---	---	AT
2	1046	524	0.001	0.002	0.997	0.002	0.001	0.002	0.001	**0.001**	205	316	579	ITT
						0.001	0.001	0.001	0.001	0.001	417	276	407	AT
3	1549	765	0.016	0.057	0.93	0.072	0.043	0.072	0.018	**0.018**	241	344	1751	ITT
						0.018	0.008	0.018	0.004	0.004	640	305	843	AT
4	1919	832	0.010	0.11	0.88	0.022	0.016	0.017	0.117	**0.022**	245	369	2100	ITT
						0.010	0.009	0.010	0.020	0.010	806	347	1346	AT
5	1880	645	0.88	0.060	0.059	0.93	0.38	0.93	0.93	0.91	232	356	1356	ITT
						0.84	0.28	0.84	0.61	0.55	670	320	996	AT
6	2350	712	0.57	0.32	0.11	0.89	0.55	0.89	0.89	0.88	260	380	1816	ITT
						0.87	0.39	0.87	0.68	0.67	814	354	1316	AT
7	1941	672	0.84	0.094	0.069	0.93	0.41	0.93	0.92	0.92	234	355	1431	ITT
						0.85	0.32	0.85	0.63	0.58	683	321	1023	AT
8	1991	707	0.79	0.12	0.091	0.90	0.43	0.90	0.90	0.90	241	362	1493	ITT
						0.85	0.34	0.85	0.64	0.60	705	28	1069	AT
9	1819	648	0.88	0.050	0.070	0.93	0.20	0.93	0.92	0.92	229	351	1303	ITT
						0.90	0.16	0.90	0.59	0.58	636	311	917	AT
10	2163	726	0.68	0.23	0.087	0.88	0.69	0.88	0.90	0.87	247	369	1629	ITT
						0.76	0.55	0.76	0.64	0.55	757	342	1180	AT

Scenario 5 is illustrated below. The first section shows the number of simulations and design characteristics as described above.

```
Simulations              =       1000
 Minimum Sample Size     =        400
 Frequency of looks (pts) =        50
 Maximum Sample Size     =       3000
 Accrual Rate            =       25.0
 Posterior Prob Win Eff  =     0.9880
 Posterior Prob Win Saf  =     0.9920
 Ratio < to Win          =     1.7500
 Diff < to Win           =     0.0287
```

The second section shows the parameters used to simulate the efficacy events. The bottom lines within the "True Efficacy Event Rate" subsection show the 2-year event rate (2.15% vs. 3.15% here) and the ratio & difference. The "True Safety Event Rate" subsection shows the event rate assumed through follow-up for the warfarin group and after day discharge for the device group. This also shows the risk ratio and risk difference.

True Efficacy Event Rate

Month	Control	Month	Treatment
True Efficacy Event Rate			
		0-proc	0.0150
0 - 6	0.0150	pr -p+6	0.7700
6 - 30	0.0150	p+7- 30	0.0076
31 - 60	0.0150	31 - 60	0.0076
60 - 6m	0.0150	60 - 6m	0.0076
6 - 12	0.0150	6m - 12	0.0076
12 - 18	0.0150	12 - 18	0.0076
18 - 24	0.0150	18 - 24	0.0076
2-year	0.0295	2-year	0.0295
Ratio =	1.0000	Diff =	0.0000

True Safety Event Rate

Annual	0.0717	Annual	0.0515
Ratio =	0.7183	Diff =	-0.0202

The final section shows the operating characteristics.

MaxN	Acc	MeanN	SD N	Mnth	SGood	StEnd	StFut	EffWn	Ratio	Diff	SFwin	E&SWin
3000	25.0	1880.	645.	81.7	0.881	0.060	0.059	0.925	0.384	0.925	0.928	0.914

CEEv	TEEv	CEExp	TEExp	CSEv	CSEv	CSExp	TSExp	0-1	1-2	2+
32.	51.	2145.	4302.	135.	202.	1882.	3925.	232.	356.	1356.

AS TREATED	AnyWn	Ratio	Diff	SFwin	E&SWin
	0.840	0.283	0.840	0.605	0.552

These show the maximum sample size (MaxN) and accrual rate (Acc) plus the mean (MeanN) and standard deviation (SD N) of the sample size and the proportions of simulated trials that stop early for predicted success (SGood), run to the maximum sample size (StEnd), and stop for futility (StFut). In this scenario 88.1% stopped for predicted success, 5.9% ran to 3000 subjects and 5.9% stopped early for futility.

The next five values show the statistical power. The probability of demonstrating efficacy non-inferiority is shown (EffWn) and further broken down by the proportion that achieve the risk ratio < 1.75 (Ratio) or risk difference < 2.87% (Diff). The probability of demonstrating superiority for safety

(SFwin) and both non-inferiority for efficacy and superiority for safety (E&SWin) are also shown. Here there is a 92.5% chance of achieving the efficacy goal, predominantly via the risk difference, a 92.8% chance of achieving the safety goal, and a 91.4% chance of achieving both.

The second line summarizes the events and exposure. CEEv, DEEv, CEExp, and DEExp show the mean number of efficacy events in the control group, efficacy events in the device group, years of exposure for efficacy in the control group, and years of exposure for efficacy in the device group. CSEv, DSEv, CSExp, and DSExp are the same for safety events.

The final three values 0-1, 1-2, and 2+ show the mean number of subjects with 0 to 1, 1 to 2, or 2 more years of exposure for successful trials. These last three figures summarize only trials in which the efficacy and safety goal are met, the idea being to relay the expected amount of follow-up times if success is declared.

The final line shows the win rates in the as treated analysis. These analyses are performed only if both the efficacy and safety goals are met in the intent-to-treat analysis.

2.15.6 Endpoints and Labeling

The following primary and secondary endpoints will be included in product labeling for the ACP device.

- **Primary Effectiveness Endpoint** (rate of ischemic stroke and peripheral thromboembolism per 100 subject years)
- **Primary Safety Endpoints** (procedure related adverse events as previously defined, as well as all-cause mortality and major bleeding)
- **Secondary Endpoints**
  - Rate of Transient Ischemic Attacks
  - Asymptomatic intracerebral or intraventricular hemorrhage

All of the above endpoints will contain inferential findings of either an acceptance or rejection of the null hypothesis (for primary endpoints), a p-value for the difference between treatments (for secondary endpoints tested in both treatment arms). Endpoints not listed above will not be summarized in product labeling.

2.15.7 Primary Analysis (REFER TO APPENDIX D)

2.15.7.1 Intent-to-Treat Analyses

Subjects are considered enrolled in the ACP clinical trial after informed consent and HIPAA authorization form or any other applicable permission form required by law has been signed and the subject has been randomized. All primary endpoint analyses will be based on the “intent-to-treat” principle. Specifically, subjects will be considered part of the intent-to-treat analysis population as long as they are randomized into the study, with no adjustment made for whether

the device was implanted, compliance with treatment, or events occurring after randomization.

2.15.8 Secondary Analyses (REFER TO APPENDIX D)

In addition to the intent-to-treat analysis, secondary analyses will be performed on the three following analysis populations (two per protocol analyses and one as-treated):

2.15.8.1 Per Protocol Analysis

a. This analysis does not count subjects who did not follow the protocol.

   This cohort is defined as all subjects who:

   - Receive the device (for subjects in the device arm) or were randomized to receive the device but did not receive the device due to a procedural adverse event or adverse event related to the pre-procedural termination of warfarin or dabigatran, such as ischemic stroke or thrombus observed in the left atrium/atrial appendage at or prior to the implant procedure.
   - As directed by the protocol, discontinue OMT(for subjects in the device arm) given the absence of flow or a minimal flow of ≤3mm into the LAA, as demonstrated by TEE, or continue OMT due to more than minimal flow present on TEE.
   - Are started on and comply with warfarin or dabigatran use (device and control arms).
   - Achieve and maintain a therapeutic INR (subjects in device and control arms who are on warfarin therapy). Have at least monthly monitoring with at least 70% of visits made and 60% time in therapeutic range (INR 2.0-3.0).

   Subjects (device and control arms) who switch to an alternative anticoagulant approved for the treatment of atrial fibrillation other than warfarin or dabigatran will be excluded from this analysis.

b. Assessment of Proof of Concept: This analysis will be conducted to assess outcomes in subjects who receive the ACP device and follow the protocol-mandated post implant medication regimen compared to subjects treated appropriately with warfarin or dabigatran. This analysis does not count subjects who are randomized to device but do not receive a device, device subjects with LAA closure who fail to stop warfarin or dabigatran at day 45, and all subjects) who deviate from therapeutic warfarin administration and monitoring (For device subjects this is from day of procedure to day 45 and for control subjects it is from day of randomization onward).

This cohort is defined as:

- Receive the device (for subjects in the device arm).
- As directed by the protocol, discontinue warfarin or dabigatran (for subjects in the device arm) given the absence of flow or a minimal flow of ≤3mm into the LAA, as demonstrated by TEE.
- Are started on and comply with warfarin or dabigatran use (device and control arms).
- Achieve and maintain a therapeutic INR (for subjects on warfarin in device and control arms). At least monthly monitoring with at least 70% of visits made and 60% time in therapeutic range (INR 2.0-3.0).

2.15.8.2 As Treated Analysis

Device subjects unable to discontinue OMT therapy may bias the intent to treat analysis toward success on the efficacy endpoint due to a sizable number of subjects in each group receiving similar treatment (success may be more difficult to achieve, however, on the safety superiority endpoint). In order to address this possibility, an "as treated" analysis will be performed that will restrict analysis of device subjects to subjects who generally experience long-term success. This analysis will compare subjects in the control arm, where applicable, against subjects in the device arm which includes:

- Received the device, discontinue OMT at six months and subsequently continue to remain off of OMT (analyzed as device)
- Subjects randomized to the control arm and continue a protocol OMT (analyzed as control)
- Subjects who are randomized to the device arm, never receive a device and continue a protocol OMT (analyzed as control)

This analysis will not necessarily disqualify subjects who violate one of the above criteria but instead will censor subjects at the earliest time point where they no longer comply with the above criteria. The primary efficacy and safety analyses will be redone using these populations and checked for level of agreement with the intent to treat population.

2.15.8.3 Secondary Analyses General Considerations

Other deviations that justify exclusion may be discovered as the trial progresses. These deviations will also disqualify subjects from the secondary analyses and will be discussed explicitly in the study's statistical analysis plan.

Subjects who are non-compliant or lost to follow-up after the procedure or after there is absence of flow or a minimal flow of ≤3mm into the LAA, as demonstrated by TEE, will not be entirely excluded from the secondary analyses. Rather, information obtained before the point of non-compliance will be

preserved in the analyses, with subsequent information excluded. In all likelihood, however, subjects who are lost to follow-up will have no subsequent information to exclude.

The intent-to-treat and secondary analyses will be compared for level of agreement. It is expected that the two subject populations will be similar; however, any substantial differences between the two will be analyzed appropriately to elucidate the cause of these differences.

2.15.9 Other Analyses (REFER TO APPENDIX D)

2.15.9.1 Subgroup Analysis

Separate analyses will be conducted for the device versus warfarin and device vs. dabigatran arms. Because subjects are stratified at or before randomization subjects randomized to device will have a label for whether they would have been prescribed warfarin or dabigatran had they been randomized to OMT. The primary efficacy and safety analyses will be performed in both groups. Parameter estimates for the risk difference and risk ratios for efficacy and safety and 95% confidence intervals will be provided. No formal statistical test will be performed since the trial is not powered to meet the objectives in each subgroup.

Furthermore the subgroup analysis will be repeated in the further sub-divided groups of subjects receiving just warfarin, just dabigatran, warfarin plus aspirin, and dabigatran plus aspirin. Additional subgroup analysis will be repeated for baseline aspirin usage.

This subgroup analysis serves a sensitivity analysis to better understand the subject populations in which the ACP devices offers the best or most robust benefit.

Gender analysis will also be performed to provide the results of the primary endpoints and inferential secondary endpoints for male/female subgroups.

An additional analysis of the major safety and effectiveness outcomes measured as a function of CHADS(2)-VASC score will be performed.

2.15.9.2 Adverse Events Categorization

Adverse Events will be categorized as serious adverse event (SAE), adverse event, or observation, as well as whether each SAE is device and/or procedure related, with separate tables reporting the same. In each table, SAE and adverse events will be summarized between the two treatment arms and compared for significant differences.

In addition, data for each subject in the trial who experienced a neurologic or embolic event, a bleeding event, or device associated thrombus will be

summarized. This will detail warfarin use, the last recorded INR, dabigatran use, and antiplatelet medication use at the time of the event.

2.15.9.3 Residual Flow in LAA

Data on all subjects in whom there is absence of flow or a minimal flow of ≤3mm into the LAA, as demonstrated by TEE at 45 days will be summarized. Since this criterion is only attained in the device arm, this analysis will only be performed on the subjects in the device arm, and will not involve comparisons between the two treatment arms. Additionally, data on subjects in the device arm with flow of less than or equal to 3mm who did not discontinue warfarin or dabigatran will be summarized. This will include the reasons the subjects did not discontinue warfarin or dabigatran.

2.15.9.4 Primary Effectiveness Component Analysis

Although the primary effectiveness endpoint for the study is the combined rate of ischemic stroke, and peripheral thromboembolism, each component rate will be analyzed separately for differences between the treatment arms. P-values will be calculated for each rate. However, since the study is not powered to examine the component differences, it is possible that overall study success may occur without significant differences among the component rates. In addition, these component rates will be summarized at separate time points. Each will be summarized at 45 days, 6 months, 1 year, 18 months and annually. In addition to the primary endpoint analysis, the composite endpoint of ischemic stroke and thromboembolism will be summarized at 45 days, 6 months, 1 year, 18 months, and annually.

2.15.9.5 Poolability Analysis

Poolability of results across sites will be analyzed to determine if differences exist among the primary safety endpoints and to determine if potential predictive covariates differ. For this poolability analysis, all centers will be compared for site differences with no centers combined in the analysis. Fisher's exact test will be used to test for comparability in terms of the primary endpoints and in terms of variables such as gender, medical history, and risk factors.

2.15.9.6 Center Effect

All of the primary and secondary analyses described above, as well as any description of baseline covariates, will be broken down by center to illustrate potential differences among the study sites.

Other analysis, such as the random effect model, may be performed to assess the possible site effect on the primary endpoints.

2.15.9.7 Analysis of Demographics

Summary statistics will be generated for all relevant demographic, medical history, and risk factor variables, and will consist of numbers and percentages of

responses in each category for discrete measures, and of means, standard deviations, number of observations, minimums, maximums, and 95% confidence intervals, as appropriate, for continuous measures. In addition, adverse event types will be summarized across treatment arms and analyzed for treatment differences for adjudicated events.

2.15.9.8 $CHADS_2$ Score Distribution

Since the ACP trial is a randomized clinical trial, there is not expected to be a difference in baseline (at the time of enrollment) CHADS score between the two treatment arms. However, the scores will be compared and tested for a significant treatment effect. If such an effect is found, an adjustment involving stratification will be made to the primary endpoint analysis. No adjustment will be made for $CHADS_2$ scores after baseline. This is because some components of $CHADS_2$, are dependent variables in this trial, and thus any differences may be due to the treatment effect that the trial is attempting to measure.

2.15.9.9 Time within therapeutic range (TTR) for INR for subjects assigned to warfarin

TTR will be calculated using the method employed in the ACTIVE W trial (Circulation, 2008). Specifically, for each subject the total number of days of TTR will be calculated and divided by the total number of treatment days in order to provide the percentage of days of TTR. Since the recording of INR after achieving therapeutic range will generally occur monthly, linear interpolation will be used to determine the number of TTR days in cases where one observation is within range while the preceding or subsequent observation is out of range.

- The ACTIVE W trial excluded certain follow-up days from this TTR calculation. These exclusions will also be followed in the ACP trial. The trial's calculation of TTR will not use follow-up data points which include:

    - Within the first seven days after warfarin is started or re-started
    - After permanent discontinuation of warfarin
    - After five days from temporary discontinuation of warfarin

Analyses will also be performed within the device and control arms to determine the percentage of time the subjects in each group were on warfarin and the percentage of time subjects were on anti-platelet medications.

2.15.9.10 Effect of Learning Curve

An analysis will also be made to assess the "learning curve" among physicians who implant the ACP device. It is hypothesized that the rate of serious adverse events and technical success may be a function of an operator's experience with the ACP procedure. In order to assess this, each operator's procedures will be categorized in groups of five according to the order in which the procedures occurred. These groups will be compared against each other in order to compare the rate of device related and procedure related adverse events. In

addition to this physician specific comparison, the groups will be pooled among all physicians in order to examine a global association of these rates with procedure order. Procedures may be categorized into larger groups, or other longitudinal analyses may be performed, if suggested by the data.

The analysis of primary endpoint events over time could potentially be sensitive to the overall length of follow-up among subjects, and therefore dependent on the number of subjects at each level of follow-up. However, this is not expected to have a major impact on the analysis of the ACP Clinical Trial.

There are four main reasons for this. First of all, the primary endpoint (events per 100 subject years) is already normalized for total follow-up, and thus the major contributor of follow-up time to the number of endpoint events would be eliminated. In addition, enrollment into the trial is not based on an index event or any other event after which endpoint events are immediately likely to occur. Also, there is no evidence of substantial increase or decrease in the endpoint component rates over time in nonvalvular AF subjects on warfarin. Finally, since the trial is randomized, any departures from homogeneity over time would likely be distributed across the two treatment arms.

Although the follow-up times are not expected to differ between the two arms, they will be compared for serious departures. If such departures are found, supplementary analyses will be performed to examine their impact on the analysis of the primary endpoint.

2.15.9.11 Handling of Missing Data

The primary efficacy endpoint is ischemic stroke or peripheral thromboembolism. Subjects are tracked continually, with data used to calculate and compare 2-year event rates in both treatment arms. The 2-year event rates are based upon a piecewise exponential model which assumes non-constant event rates over the course of the study.

The primary safety endpoint is long-term composite rates of all-cause mortality and major bleed. Rates are compared in a manner similar to the efficacy endpoint comparison. Both primary analyses are intent-to-treat analyses where subjects are considered a part of the group to which they were randomized. Subject data is considered a part of the efficacy analysis until

(a) They experience their first efficacy event,
(b) They die,
(c) They become lost-to-follow-up, or
(d) The study ends.

All subjects are tracked until the study ends rather than being followed for a fixed maximum time period (e.g. 2 years). Subjects meeting criteria (a) are treated as experiencing an event. Subjects first reaching (b), (c), or (d) are considered censored.

Likewise subjects contribute data to the safety analysis until
(a) They experience a safety event (including death),
(b) They become lost-to-follow-up, or
(c) The study ends

Subjects reaching (b) or (c) before experiencing an event are considered censored. Subjects who experience a non-fatal event contributing toward the efficacy endpoint are still followed for safety and vice versa. The operating characteristics in the original design document and those shown below assume a 5% dropout rate per year in both groups.

The primary efficacy and safety analysis assume that all censored subjects contribute data until their time of last visit. It is assumed that all censoring is non-informative censoring. If so, the parameter estimates for each group are unbiased. Such an analysis is also assumed during each interim analysis used to select the sample size. At the conclusion of the trial, a variety of sensitivity analyses will be performed in case censoring is not non-informative. There is a concern that subjects who are lost-to- follow-up may not be non-informatively censored.

First, the piecewise model for efficacy will be analyzed for differences in lost-to-follow- up rates by group and by period. This will include illustrating the censoring pattern by showing Kaplan-Meier curves of time-to-lost-to-follow by group. The primary analysis will also be repeated using Bayesian multiple imputation. Using a technique similar to that used at each interim analysis for subjects being tracked, posterior distributions for the event rates will be used to draw event times for all lost-to-follow-up subjects and to calculate the predictive probability of success had the lost-to-follow-up subjects been tracked until the study's end. By repeating this process 10,000 times, it will have the effect of including missing subjects in the final analysis and will incorporate the uncertainty that surrounds the estimates of the times they would have experienced an event. In addition, Cox proportional hazards models will be performed that include baseline and time-to-event variables such as age, gender, CHADS2 components, coagulation parameter test values, and any baseline variable subsequently discovered to have an overall association with the study endpoint. The results of these models will compare the coefficient and 95% confidence interval for the hazard ratio of the treatment group variable, as well as explore any interactions between baseline covariates and treatment effect. The primary analysis can also be repeated assuming subjects have an event instead of being lost-to-follow-up. This is an extreme situation analysis in which assumes that being lost-to-follow-up is a likely indicator of experiencing an event. Each of these sensitivity analyses will be performed for both the efficacy analysis and the safety analysis, in the intent to treat study populations. Sensitivity analyses may be performed for other analyses as deemed appropriate.

Additionally a worse case and tipping point sensitivity analyses will also be performed.

2.15.9.12 Worst–case analysis

Throughout the duration of the ACP clinical trial all efforts will be made to minimize any expected lost to follow-up. For the worst case scenario analysis, we will consider subjects in the device group as having events at the time they are declared lost-to-follow-up and subjects in the control group as having their follow-up end with no event at the time they are declared lost-to-follow-up.
This analysis will be performed once for the efficacy analysis and once for the safety analysis.

For the efficacy analysis, a worst case scenario dataset will be created. This dataset will consist of:

- Observations which are unchanged for subjects not lost to follow-up or lost to follow-up in the control group.
- Observations which are modified, for subjects lost to follow-up in the device group, to events experienced at the time of discontinuation

For the purposes of the sensitivity analysis, “Lost to follow-up” is defined as any subject who discontinues before the trial’s conclusion without an endpoint event, regardless of the reason given for discontinuation.

This dataset will then be used with the piecewise exponential model for the efficacy endpoint. Using this dataset, posterior distributions for each group’s 2-year event rate, their ratio, and their difference will be calculated. The primary set of tests will be performed according to protocol.

Lost-to-follow-up subjects will be analyzed in an analogous manner in the safety analysis. Lost-to-follow-up device group subjects will be considered to have had a safety event at the time they were lost. Lost-to-follow-up control group subjects will be considered not to have had an event but have their exposure ending at the time they are lost to follow-up. Data from all other subjects (subjects that are not lost to follow-up) will remain unchanged, with the safety analysis will be performed as described in the protocol.
Tipping point analysis- Furthermore we will perform a tipping point analysis for both the safety and efficacy endpoints.

The sufficient statistics for the safety analysis are the total number events (Ev) and the total exposure (Expos) in each group. The primary test for safety is

$$\Pr\left(\frac{\gamma_T}{\gamma_C} < 1.0 \mid Ev_T, Ev_C, Exp_T, Exp_C\right) \geq 0.992$$

which is equivalent to testing whether the two-sided 98.4% credible interval for the hazard ratio is entirely less than 1.0.

The primary analysis will be performed considering lost-to-follow-up subjects as censored. For the tipping point analysis, the exposure times in both groups will be considered fixed. The number of events in each group can possibly range from a minimum of Ev_T and Ev_C (the observed number of safety events in the treatment and control groups, respectively, assuming lost-to-follow-up subjects are censored without events) to Ev_T+M_T and Ev_C+M_C (the observed number of safety events plus the number of subjects lost-to-follow-up in each group which combined with the fixed exposure times assumes that all lost-to-follow-up subjects had events at the exact time they were considered lost-to-follow-up).

We will repeat the safety analysis for every pair of events $\{Ev_T, Ev_T+1, \ldots Ev_T+M_T\} \times \{Ev_C, Ev_C+1, \ldots, Ev_C+M_C\}$. We will show a plot that illustrates which pairs lead to successful safety claims, $Pr(\gamma_T / \gamma_C < 1.0) \geq 0.992$ shown with green dots, and which do not shown with red dots, thus producing a boundary of trials that meet the predetermined safety criteria and those that do not.

We will perform a similar analysis for the primary efficacy analysis. This is slightly complicated because the statistical model uses a piecewise exponential. Therefore all events are not exchangeable – they can have slightly different effects depending in which segment of the piecewise model the event is assumed to have occurred.

We observe number of events and total exposure time within each treatment group (g) x time period (T) then use these to calculate posterior distributions for each time segment's event rates, $\lambda_{g,T}$. Then we combine these posterior distributions to calculate the posterior distribution for the probability of an event by 2 years for the treatment group

$$\begin{aligned}\pi_D &= \Pr(\text{Event by 2 years in ACP Device Group}) \\ &= 1-\exp\left(-\left(10\lambda_{D,0}+7\lambda_{D,1}+13\lambda_{D,2}+30\lambda_{D,3}+122.5\lambda_{D,4}+182.5\lambda_{D,5}+182.5\lambda_{D,6}+182.5\lambda_{D,7}\right)\right)\end{aligned}$$

and control groups

$$\begin{aligned}\pi_C &= \Pr(\text{Event by 2 years in Control group}) \\ &= 1-\exp\left(-\left(6\lambda_{C,1}+24\lambda_{C,2}+30\lambda_{C,3}+122.5\lambda_{C,4}+182.5\lambda_{C,5}+182.5\lambda_{C,6}+182.5\lambda_{C,7}\right)\right)\end{aligned}$$

Finally we use the posterior distributions for λ_T and λ_C to calculate the risk ratio and risk difference. If $Pr(\lambda_D/\lambda_C < 1.75) > 0.988$ and/or $Pr(\lambda_D-\lambda_C < 2.87\%) > 0.988$ then the trial has reached the non-inferiority threshold.

When considering from 0 to MT and 0 to MC of the lost-to-follow-up subjects as having events, it is unlikely that the timing of the event will be the difference between a successful vs. unsuccessful trial, e.g. assuming a patient lost-to-

follow-up during the first segment has an event vs. assuming a patient lost-to-follow-up in the final segment has an event has negligible effect on the final posterior probability of non-inferiority. Therefore it is unlikely that assuming an event occurs in one segment vs. another will be the difference in meeting or failing to meeting the efficacy success criteria.

Nevertheless, we will explore all possibilities. Assuming we observe Ev_T and Ev_C efficacy events in the treatment and control groups, respectively, and M_T and M_C subjects are lost-to-follow-up, we will perform the analysis for every pair of possible efficacy events: $\{Ev_T, Ev_T+1, \ldots Ev_T+M_T\} \times \{Ev_C, Ev_C+1, \ldots, Ev_C+M_C\}$.

Here, however, an event may occur in any one of 8 treatment segments of the piecewise exponential or any one of 7 control segments of the piecewise exponential.

For example, if there are 3 subjects with missing data, 2 might be lost-to-follow-up in the 30-60 day period and the other might be lost-to-follow-up in the 12-18 month period. We will perform the analysis assuming 0, 1, 2, and 3 of the lost-to-follow-up subjects have events. Our imputation step when assuming 1 event out of the 3 lost-to-follow-up subjects will perform the analysis as if the event occurred in the 30-60 day period, and then repeat it assuming it occurred in the 12-18 day period. Instead of the plot showing a simple green or red for successfully meeting the efficacy endpoint vs. failing to meet the efficacy endpoint, we will show the proportion of imputed trials (out of 3 possible here) that result in trials demonstrating non-inferiority according to the prespecified rule. According to our exploration it is unlikely that the placement of a missing event will determine whether or not the success definition is met. The number of event, far more than their location, is the determinant.

Therefore the final analysis will be presented as a grid showing all possible study outcomes from Ev_T to Ev_T+M_T treatment events vs. Ev_C to Ev_C+M_C control events. Most points are likely to show simply green (for all possible combinations of those event counts meeting the non-inferiority criterion) or red (for all possible combinations of those event counts failing to meet the non-inferiority criterion). But some points may show a proportion indicating the probability that combination of treatment and control events results in a successful trial in the rare event that the timing of the assumed events determines success vs. failure.

Version 9.0 or higher of the SAS® statistical software package or R 2.14 or other widely accepted statistical software will be used to provide all non-Bayesian statistical analyses.

2.16 ADVISORY COMMITTEES

2.16.1 STEERING COMMITTEE

The Steering Committee will be composed of medical practitioners who are experts in the field of the proposed indication for the study. The Committee will serve as an advisory board during the course of the study as well as after its completion. Specific responsibilities of the members will depend upon the consulting expertise needed by the Sponsor.

2.16.2 DATA SAFETY MONITORING BOARD AND CLINICAL EVENTS COMMITTEE (REFER TO APPENDIX D)

Both an independent Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC) will be utilized to regularly review study progress with regard to safety. The CEC will be blinded to subject's treatment assignment. Members of these boards cannot be investigators on the ACP Clinical Trial. Board membership includes: cardiologists, neurologists, and biostatisticians. The primary responsibilities of the DSMB and CEC include:

- Review and refine adverse event definitions as necessary during the conduct of the clinical investigation
- Review and adjudicate adverse events and primary endpoints as they occur over the course of the clinical investigation
- Review and validate the subject sample (i.e., review inclusion/exclusion deviations and other protocol deviations)
- Provide oversight for issues affecting general subject welfare
- Recommend premature study termination

At any time during the course of the study, the DSMB and CEC may offer opinions or make formal recommendations concerning aspects of the study that impact subject safety (e.g., safety-related protocol changes or input regarding adverse event rates associated with the investigational study). Additionally, the DSMB and CEC may act as an advisory panel for questions regarding informed consent, subject enrollment, protocol implementation, study endpoints, data discrepancies, and other issues that may present during the course of the study.

2.16.3 ECHO CORE LAB

An independent Echo Core Lab/Board will analyze all TEEs and TTEs as required during the trial. Members of the Echo Core Lab will have no affiliation with the ACP Clinical Trial.

2.16.4 BRAIN IMAGING CORE LAB

An independent core lab will be utilized to review any MRI and/or CT (if performed) conducted at baseline and at designated follow up visits to determine endpoint event occurrence. Members of the Brain Imaging Core Lab will have no affiliation with the ACP Clinical Trial.

2.16.5 BLOOD WORK CORE LAB (REFER TO APPENDIX D)

An independent core lab will be utilized to perform baseline hematology and coagulation tests (as described in section 2.9). Members of the Blood Work Core Lab will have no affiliation with the ACP Clinical Trial.

2.17 STUDY MANAGEMENT

2.17.1 CLINICAL PROJECT MANAGEMENT

An AGA Medical clinical project team will be developed and trained to select qualified investigators, train investigative sites, monitor the clinical trial, ensure IRB approvals and renewals are obtained, and to inform the IRB and FDA of any significant new information about the clinical trial. The team will adhere to AGA Medical LLC internal procedures, 21 CFR parts 54, 56, 812, and all other applicable regulations.

2.18 ADMINISTRATIVE REQUIREMENTS

2.18.1 INVESTIGATOR SELECTION AND TRAINING

AGA Medical will select qualified investigators and provide them with the necessary information and training on the investigational plan and ACP implantation procedure in order for them to conduct the investigation properly. Investigators who are selected to participate in the ACP trial will be required to attend SimSuite training (procedure simulation which is specific to implantation of the ACP device) and didactic training on the ACP protocol and implantation procedure. Other training may be provided as necessary on an individual or group basis.

2.19 TRAINING THROUGHOUT THE STUDY

Training may be conducted throughout the course of the clinical trial if changes are made to the investigational plan, for non-compliance, and/or for changes in site personnel during the clinical trial. Training may include investigator meetings, additional proctoring, conference calls, and/or web-based training sessions.

2.20 PROTOCOL ADHERENCE AND AMENDMENTS

2.20.1 PROTOCOL DEVIATION

A protocol deviation is any deviation from the investigational plan. Deviations from the investigational plan will be recorded on the Deviation Case Report Form (CRF). If applicable, the site is responsible for notifying their IRB of any deviations. AGA Medical should be informed of all IRB notifications.

Deviations from the investigational plan include but are not limited to:

- Required testing not completed or done outside window
- Subject follow-up not completed or completed outside of window
- SAE not reported

- Study-required testing done prior to signing the Informed Consent Form
- Other Informed Consent issues
- Inclusion/exclusion criteria not met for enrolled subjects
- Enrolling subjects after an IRB lapse
- Continued collection of subject study related data during an IRB lapse

Investigator compliance will be continuously assessed by the AGA Clinical Affairs management team and appropriate corrective action will be taken when necessary.

2.20.2 PROTOCOL AMENDMENTS

Protocol amendments may occur during the course of the study and will be reviewed prior to implementation to determine if the changes affect the: validity of the data; subject risk-to-benefit ratio; scientific soundness of the investigational plan; or the rights, safety, or welfare of the human subjects involved in the clinical trial.

Protocol amendments that affect any of the above criteria will require FDA and IRB approval prior to implementation. Protocol amendments that do not meet the criteria above will be reported to the FDA according to 21 CFR 812.35.

2.20.3 EMERGENCY DEVIATIONS FROM INVESTIGATIONAL PLAN

If a deviation from the investigational plan is necessary to protect the life or physical well-being of a subject in an emergency, the investigator must notify AGA Medical LLC and the appropriate IRB within five (5) working days.

2.20.4 CONFIDENTIALITY

All subject information collected during the course of this study will be kept strictly confidential according to applicable country-specific laws and regulations. All data and information concerning subjects and their participation in this study are considered confidential by Sponsor, and its affiliates (located in the U.S.A. and European Economic Area (EEA), Canada, and other countries), and other people who work for Sponsor to provide services related to the device and this study (collectively referred to as “AGA”). All public reporting of the results of the study will eliminate identifiable references to the subjects. Information on paper will be kept in secured locations. Electronic information will be kept on password-protected computers.

Personal data, including medical and health information, will be processed both by computer and manually, during and after the study by Sponsor, and its affiliates, its designated third party data processors, the IRB, the institution conducting the study, the study doctors and other healthcare personnel involved in the study for the purposes of this study. The electronic data stored for this study will be kept in an Sponsor database, in compliance with part 11 of the us code of federal regulations. Subject data will not

contain details of study subject identity. The data will be stored on a secure server and backed up routinely. All records and reports required by or prepared in connection with this study shall be maintained by the institution and the site principal investigator in a secure location for a minimum period of 2 years post approval or longer as may be otherwise required by local law. Personal data will be key-coded to prevent subject identification, except by the institution, study doctors and other healthcare personnel involved in the study, if necessary for the purpose of the study, for regulatory inspections, and to comply with sponsor reporting obligations.

Study subjects have a right to gain access and to correct inaccuracies in information about them as permitted by applicable law. In order to help keep subject medical records and personal information confidential only certain authorized investigators and sponsor personnel, or approved contracted agents of sponsor, will have access to confidential records. These include researchers in the hospital who are part of this study, sponsor and its affiliates and representatives that perform study-related services who may be located in the U.S.A., Canada, European Economic Area (EEA) and other countries. The IRB and other regulatory authorities also have the right to inspect and copy records pertinent to this study. It is necessary for them to review study data, portions of study subject records and information so that they can follow the study progress, which may include without limitation:

- monitor the accuracy and completeness of the study
- perform scientific analysis and develop the medical product
- and/or obtain approval to market the medical products in the USA, Canada, EEA, and other countries.

Any information about subjects that leaves the institution conducting the study will be modified to remove certain information that could identify the subject (e.g., subject's name, age on the day of enrollment, address, and hospital number) and only be identifiable by a study id code. Study data provided to sponsor that is published in medical journals and/or presented at scientific conferences will not allow the identification of study subjects.

The results of the study will be made available to sponsor and its affiliates (located in the U.S.A., EEA, Canada, and other countries) and other people who work for sponsor to provide services related to the device and this study and study center.

A summary of the information on all subjects may be provided to governmental agencies (including regulatory agencies), regulatory authorities in the U.S.A., Canada, EEA and other countries who may also need to review study data and portions of medical records. Results from this study may also be published in scientific journals or presented at conferences as an oral or poster presentation; however, the identity of a study subject will not be disclosed.

2.20.5 INFORMED CONSENT COMPLIANCE

Informed consent must be obtained using the IRB approved informed consent and according to the IRB's requirements. Informed consent deviations include but are not limited to:

- Failure to consent subject
- Failure to obtain subject signature
- Failure to obtain date/time of subject signature (if applicable)
- Failure to obtain signature of person conducting the informed consent process
- Failure to obtain witness signature, if applicable
- Unapproved consent form used
- Failure to obtain HIPAA Authorization

2.21 CLINICAL STUDY COMPLIANCE

AGA Medical will review and monitor investigator compliance and determine if there is a need for corrective action based on the severity and/or trends in non-compliance to the signed agreement with AGA Medical LLC, the investigational plan, the applicable regulations, or any conditions of approval imposed by the reviewing IRB or FDA (21 CFR 812.46 (a)). Depending on the severity and/or trend in non-compliance, the investigator may receive a formal warning, or retraining through a site visit or conference call. AGA Medical may terminate the investigator's participation in the clinical trial or suspend enrollment if repeat non-compliance occurs.

2.22 INSTITUTIONAL REVIEW BOARD

All IRBs must comply with applicable IRB regulation (21 CFR 56) and IDE regulations (21 CFR 812) in reviewing and approving device investigations.

2.22.1 RESPONSIBILITIES

An IRB shall safeguard the rights, safety, and well being of all study subjects.

2.22.2 COMPOSITION

The IRB shall be composed of members meeting the minimum requirements set forth in 21 CFR 56.107.

2.22.3 INITIAL IRB APPROVAL

Prior to shipment of investigational devices for this study, AGA Medical will require documentation of IRB approval of the investigational plan and subject informed consent.

2.22.4 ANNUAL IRB RENEWAL

An IRB 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 (21 CFR 56.109).

2.23 DEVICE ACCOUNTABILITY

Upon receipt of the ACP, investigators will maintain the following accurate, complete, and current records relating to device accountability. Records of receipt, use, or disposition of device including:

- Type and quantity of devices
- Date of receipt
- Serial number
- Names of all persons who received, used or disposed of each unit, and
- Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of

All investigational products must be accounted for and returned at the end of the trial.

2.23.1 TECHNICAL INCIDENTS

Complete a Technical Incident CRF if the ACP or the Delivery System does not perform to your expectations or you experience any technical malfunctions.

2.24 DATA ENTRY AND CRF SUBMISSION

The Principal Investigators and/or authorized study center designees may complete the CRFs.

- The investigator and site staff will be trained on data entry and CRF submission during the site initiation visit
- The investigator is responsible for assuring accuracy, completeness, and timeliness of the CRFs sent to AGA Medical
- Data reported on the CRFs should be consistent with the source documents or the discrepancies should be explained
- Manual or automatic Data Clarification Forms (DCF) will be generated by AGA Medical for incomplete or inaccurate data points and sent to the site for completion

2.25 DATA MANAGEMENT

A Data Management Plan (DMP) will be completed as part of the database development. The DMP will be updated as necessary during the clinical trial. A clinical database will be developed and validated for the ACP clinical trial. A record will be created in the database for each subject in the clinical trial. Data collected during this clinical trial will be analyzed, and submitted in the form of a Premarket Approval (PMA).

2.26 INSTITUTIONAL AUDITS

The ACP clinical trial will be audited to internal and external regulations, standards, and procedures to assess compliance. The investigator will permit study-related auditing and inspections of all study-related documents by the IRB, government regulatory agencies, and

AGA Medical. The investigator will allocate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

2.27 CONFLICT OF INTEREST

Investigators who have a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with AGA Medical and applicable federal, state and local laws and regulations. Investigators will be required to submit a financial disclosure prior to study participation.

2.28 PUBLICATION POLICY

No study results obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of AGA Medical. Investigators are obligated to follow the AGA Medical publication policy.

2.29 ECONOMIC AND QUALITY OF LIFE SUB-STUDY (REFER TO APPENDIX D)

In conjunction with the pivotal phase of clinical study, the costs and benefits of treatment will be evaluated through an economic and quality of life analysis . Medical resource use, cost and health-related quality of life within the trial period will be compared between treatment groups. If ACP therapy is found to be effective, its long term cost-effectiveness analysis will be assessed. The economic and quality of life analysis will be fully integrated into the clinical trial, with a common informed consent form and collection of subject reported resource use in the case report form. Hospital bills reporting hospital care for study subjects during the study period will also be collected at least through 2 years and until the study is completed.

2.30 REFERENCES

1. [No authors listed] Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994 Jul 11;154(13):1449-57. Erratum in: Arch Intern Med
2. [No authors listed] Stroke Prevention in Atrial Fibrillation Study: Final Results. Stroke Prevention in Atrial Fibrillation Investigators. *Circulation*. 1991 August;84(2):527-39
3. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus Aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006 Jun 10;367(9526):1903-12
4. Agmon Y, Khandheria BK, Gentile F, Seward JS. Echocardiographic assessment of the left atrial appendage. *J Am Coll Cardiol*. 1999;34;1867-1877
5. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks (Review); The Cochrane Collaboration
6. Alizadeh A, Maeki M, Bassiri H, Alasti M, Emkanjoo Z, Haghjoo M, Arya A, Bagherzadeh A, Faze Lifar A, Sadr-Ameli MA. Evaluation of atrial thrombus

formation and atrial appendage function in subjects with pacemaker by transesophageal echocardiography. *Pacing Clin Electrophysiol*. 2006 Nov;29(11):1251-4.
7. Almahameed ST, Khan M, Zuzek RW, Juratli N, Belden WA, Asher CR, Novaro GM, Martin DO, Natale A. Left atrial appendage exclusion and the risk of thrombolembolic events following mitral valve surgery. *J Cardiovasc Electrophysiol*. 2007 Apr;18(4):364-6
8. American Heart Association. *Stroke Statistics*. Dallas, Tex: American Heart Association; 2000
9. Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the Prevention of Systemic Embolism in Subjects with Nonvalvular Atrial Fibrillation: A Meta-analysis. *Heart*. 2008 Jan 20
10. Arch Intern Med. 1994 Jul 11;154(13):1449-57. Erratum in: Arch Intern Med
11. Atritech Incorporated. Watchman LAA (PMA P080022). http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4434b1-09.pdf
12. Bertaglia E et al. Early complications of pulmonary vein catheter ablation for atrial fibrillation: A multicenter prospective registry on procedural safety. *Heart Rhythm*. 2007;4:1265-1271.
13. Bhargava M et al. Impact of age on the outcome of pulmonary vein isolation for atrial fibrillation using circular mapping technique and cooled-tip ablation catheter: A retrospective analysis. *Journal of Cardiovascular Electrophysiology*. 2004;15:8-13.
14. Biosense Webster. ThermoCool (PMA P030031). http://www.accessdata.fda.gov/cdrh_docs/pdf3/P030031S011b.pdf
15. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical subjects with atrial fibrillation. *Ann Thorac Surg*. 1996;61:755-9.
16. Bourke J et al. Pulmonary vein ablation for idiopathic atrial fibrillation: Six month outcome of first procedure in 100 consecutive patients. *Heart*. 2005;91:51-57.
17. Bunch T et al. Outcomes after cardiac perforation during radiofrequency ablation of the atrium. *Journal of Cardiovascular Electrophysiology*. 2005;16:1172-1179.
18. Calkins H et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: Two systematic literature reviews and meta-analysis. *Circulation Arrhythmia and Electrophysiology*. 2009;2:349-361.
19. Cappato R et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation*. 2005;111:1100-1105.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.Comparison of Outcomes Among Patients Randomized to Warfarin Therapy According to Anticoagulant Control. Results From SPORTIF III and V: Harvey D. White, DSc; Michael Gruber, MSc; Jan Feyzi, MS; Scott Kaatz, DO; Hung-Fat Tse, MD; Steen Husted, MD; Gregory Albers, MD. *Arch Intern*. 2007;163(3):239-245.
21. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin; RE-LY Steering Committee and

Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009 Sep 17;361(12):1139-51.
22. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991 Aug;18(2):349-55.
23. Cruz-Gonzalez I, Martin MJ, Garcia E. Thrombus formation after left atrial appendage exclusion using an Amplatzer cardiac Plug Device. *Catheter Cardiovasc Interv*. 2011 Nov 15;78(6):970-3.
24. Crystal E, Connolly SJ. Role of oral anticoagulation in management of atrial fibrillation. *Heart.* 2004 Jul;90(7):813-7.
25. Dagres N et al. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: Still cause for concern? *Journal Cardiovascular Electrophysiology*. 2009;20:1014-1019.
26. Dans AM, Ezekowitz M, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial (abstract 1161). *Eur Heart* J 2011; 32 (Suppl 1): 6.
27. Davidson E, Weinberger I, Rotenberg Z, Fuchs J, Agmon J. Atrial fibrillation: Cause and time of onset. *Arch Intern Med*. 1989 Feb 149:457-59.
28. Deisenhofer I et al. Long term outcome after segmental electric isolation of pulmonary veins in paroxysmal atrial fibrillation and implications for re-ablation procedures. *European Heart Journal*. 2004;25:277. (Abstract P1644)
29. Della Bella P et al. Long-term follow-up after radiofrequency catheter ablation of atrial ablation: Role of the acute procedure outcome and of the clinical presentation. *Europace*. 2005;7:95-103.
30. Demkow M, et al. Transcatheter closure of left atrial appendage with the Amplatzer Cardiac Plug in patients with atrial fibrillation and high risk of thromboembolic events – early experience. *Kardiol Pol* 2010; 68: 250-254.
31. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). *Chest*. 2012;141(2 Suppl):e326S-50S.
32. Essebag V et al. Non-inducibility post-pulmonary vein isolation achieving exit block predicts freedom from atrial fibrillation. *European Heart Journal*. 2005;26:2550-2555.
33. Ezekowitz, MD. The Management of Patients with Atrial Fibrillation. *N Engl J Med*. 1992;327:1406-1412.
34. Ezekowitz MD, James KE, Nazarian SM, Davenport J, Broderick JP, Gupta SR, Thadani V, Meyer ML, Bridgers SL. Silent cerebral infarction in subjects with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *Circulation*. 1995 Oct 15;92(8):2178-82.
35. Fagundes R et al. Safety of single transseptal puncture for ablation of atrial fibrillation: Retrospective study from a large cohort of patients. *Journal of Cardiovascular Electrophysiology*. 2007;18:1277-1281

36. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol*. 2011 Mar 15;57(11):e101-98.
37. Fuster V, Ryden LE, Cannom D ACC/AHA/ESC Guidelines for the management of subjects with atrial fibrillation. A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology Committee for practice guidelines (Writing committee to revise the 2001 Guidelines for management of subjects with atrial fibrillation). *J Am Coll Cardiol*. 2006; 48:e149
38. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001 Jun 13;285(22):2864-70.
39. Gajewski J, Singer R. Mortality in an insured population with atrial fibrillation. *JAMA*. 1981 Apr 17;245(15):1540-44.
40. Garcia-Fernandez MA, Perez-David E, Quiles J, Peralta J, Garcia-Rojas I, Bermejo J, Moreno M, Silva J. Role of left atrial appendage obliteration in stroke reduction in subjects with mitral valve prolapse: A transesophageal study. *J Am Coll Cardiol.* 2003 Oct 1;42(7):1253-8
41. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003 Nov 26;290(20):2685-92
42. Go AS, Hylek EM, Philips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. *JAMA.* 2001; 285:2370-2375.
43. Golstein LB et al. Primary prevention of ischemic stroke. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association Stroke 2001; 32: 280-99
44. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011 Sep 15;365(11):981-92. Epub 2011 Aug 27.
45. Gullov AL, Koefoed BG, Patersen P. Bleeding complications to Long-Term Oral Anticoagulation therapy. *J Thromb Thrombolysis*. 1994;1(1);17-25
46. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus Aspirin for preventing stroke in subjects with atrial fibrillation. *Ann Intern Med*. 2007 Oct 16;147(8):590-2
47. Hsu L et al. Catheter ablation for atrial fibrillation in congestive heart failure. *New England Journal of Medicine*. 2004;351:2373-2383.

48. Frost L, Engholm G, Johnsen S, Møller H, Husted S. Incident stroke after discharge from the hospital with a diagnosis of atrial fibrillation. *Am J Med*. 2000 Jan;108(1):36-40
49. Israel C, Gronefeld G, Ehrlich J, Li Y, Hohnloser S. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol.* 2004 Jan 7;43(1):47-52.
50. Jais P et al. Atrial fibrillation ablation vs antiarrhythmic drugs: A multicenter randomized trial. *Heart Rhythm*. 2006;3:1126-1128. (Late-breaking clinical trial abstract LBA-6565 presented at 2006 Heart Rhythm Society).
51. Jais P et al. Technique and results of linear ablation at the Mitral Isthmus. *Circulation*. 2004;110:2996-3002.
52. Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham Study. Am Heart J. 1983 Aug;106(2):389-96.
53. Kumagai K et al. Comparison of 2 mapping strategies for pulmonary vein isolation. *Circulation Journal*. 2005;69:1496-1502.
54. Lam, YY, Yip GW, YU CM, Chan WW, Cheng BC, Yan BP, Clugston R, Yong G, Gattorna T, Paul V. Left atrial appendage closure with Amplatzer Cardiac Plug for stroke prevention in atrial fibrillation: Initial Asia-Pacific experience. *Catheter Cardiovasc Interv*. 2011 May 3. doi: 10.1002/ccd.23136
55. Liu X et al. Recurrent atrial tachycardia and atrial fibrillation after circumferential pulmonary vein ablation: What's the difference? *Chinese Medical Journal*. 2005;118:1773-1778.
56. Marchlinski F et al. Efficacy and safety of targeted focal ablation versus PV isolation assisted by magnetic electroanatomic mapping. *Journal of Cardiovascular Electrophysiology*. 2003;14:358-365.
57. Marrouche N et al. Circular mapping and ablation of the pulmonary vein for treatment of atrial fibrillation: Impact of different catheter technologies. *Journal of the American College of Cardiology*. 2002;40:464-474.
58. Martinez A, et al. Percutaneous closure of Left Atrial Appendage in patients with atrial fibrillation with the Amplatzer Cardiac Plug Device. Preliminary Data, *Revista Chilena de Cardiologia* 2010 Vol. 29 N1.
59. Matthew W. Reynolds, PhD; Kyle Fahrbach, PhD; Ole Hauch, MD; Gail Wygant, RN, MS; Rhonda Estok, RN, BSN; Catherine Cella and Luba Nalysnyk, MD, MPH. Warfarin Anticoagulation and Outcomes in Patients With Atrial Fibrillation. A Systematic Review and Metaanalysis; *Chest*. 2004;126:1938-1945.
60. Meerkin D, et al. Initial Experience with the AMPLATZER Cardiac Plug for Left Atrial Appendage Occlusion. JACC 2011, Volume 57, Issue 14.
61. Miller VT, Rothrock JF, Pearce LA, Feinberg WM, Hart RG, Anderson DC. Ischemic stroke in subjects with atrial fibrillation: effect of Aspirin according to stroke mechanism. Stroke Prevention in Atrial Fibrillation Investigators. *Neurology*. 1993 Jan;43(1):32-6
62. Nademanee K et al. A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. *Journal of the American College of Cardiology*. 2004;43:2044-2053.

63. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011 Sep 8;365(10):883-91.
64. Oral H et al. Incremental value of isolating the right inferior pulmonary vein during pulmonary vein isolation procedures in patients with paroxysmal atrial fibrillation. *PACE*. 2004;27:480-484.
65. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block, PC, Omran H, Bartorelli AL, et al. Percutaneous left atria appendage transcatheter occlusion (PLAATO System) to prevent stroke in high risk subjects with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol*. 2005 Jul 5;46(1):9-14
66. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block, PC, Omran H, Bartorelli AL, et al. Percutaneous left atria appendage transcatheter occlusion (PLAATO System) to prevent stroke in high risk subjects with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol*. 2005 Jul 5;46(1):9-14
67. Page R, Wilkinson W, Clair W, McCarthy E, Pritchett E. Asymptomatic arrhythmias in subjects with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation*. 1994 Jan 89(1):224-27.
68. Pappone C et al. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: Efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation*. 2001;104:2539-2544.
69. Pappone C et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation. Outcomes from a controlled nonrandomized long-term study. *Journal of the American College of Cardiology*. 2003;42:185-197.
70. Pappone C et al. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: A prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. *Circulation*. 2004;110:3036-3042.
71. Park JW, et al. (2011), Left atrial appendage closure with Amplatzer Cardiac Plug in Atrial Fibrillation: Initial European experience. *Catheterization and Cardiovascular Interventions*, 77: 700–706.
72. Park JW, Leithauser B., Schmid, M., Khattab, A., Gloeckler, S., Sperl, T., Kasch, F. and Meier, B. (2011) Dual Center Experience with Different Strategies of Left Atrial Appendage Closure with Amplatzer Cardiac Plug for Prevention of Stroke in Atrial Fibrillation. Presented at UHK Mayo Clinic Asia Cardiovascular Summit. 26-7 March (Hong Kong).
73. Park JW, et al. AMPLATZER® Cardiac Plug Post-Market Registry Interim Results. Presented at CSI-Congenital and Structural Interventions June 2011.
74. Park JW, et al. Interim Data from AMPLATZER® Cardiac Plug Registry. Presented at TCT- Transcatheter Cardiovascular Therapeutics Conference, November 7-11, 2011. JACC 2011, Volume 58, Issue 20, Suppl B, B33.

75. Petersen P, Boysen G Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomized trial of warfarin and Aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989 Jan 28;1(8631):175-9
76. Phillips S, Whisnant J, O'Fallon M, Frye R. Prevalence of cardiovascular disease and diabetes mellitus in residents of Rochester, Minnesota. Mayo Clin Proc 1990 March 65:344-359.
77. PRADAXA Prescribing Information and Medication Guide. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf
78. PREVAIL trial. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01182441. Accessed June 01, 2012.
79. Purerfellner H et al. Short- and long-term experience in pulmonary vein segmental ostial ablation for paroxysmal atrial fibrillation. *Indian Pacing and Electrophysiology Journal*. 2006;6:6-16.
80. Rodes-Cabau J, Champagne J, Bernier M. Transcatheter Closure of the Left Atrial Appendage: Initial Experience with the Amplatzer Cardiac Plug Device. *Catheterization and Cardiovascular Interventions* 76:186-192 (2010)
81. Rodgers M et al. Curative catheter ablation in atrial fibrillation and typical atrial flutter: Systematic review and economic evaluation. *Health Technology Assessment*. 2008;12(34).
82. Saad E et al. Pulmonary vein stenosis after radiofrequency ablation of atrial fibrillation: Functional characterization, evolution, and influence of the ablation strategy. *Circulation*. 2003;108:3102-3107.
83. Santoro, G et. al. The Next Step on the Learning Curve of Percutaneous Left Atrial Appendage Occlusion, presented at International Symposium on Progress in Clinical Pacing, Rome December 2010
84. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. EAFT (European atrial fibrillation trial) study group. *Lancet* 1993 Nov 20:342(8882):1255-62
85. Shah D et al. Curative catheter ablation of paroxysmal atrial fibrillation in 200 patients: Strategy for presentations ranging from sustained atrial fibrillation to no arrhythmias. PACE. 2001;24:1541-1558.
86. Shah D et al. Nonpulmonary vein foci: Do they exist? *PACE*. 2003;26:1631-1635.
87. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, Miskel G, Almany S, Holmes DR. Initial world wide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2007 Apr 3;49(13):1490-5
88. Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, Nakai T, Reisman M, DiMario C, Block P, Kramer P, Fleschenberg D, Krumsdorf U, Scherer D. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk subjects with atrial fibrillation: early clinical experience. *Circulation*. 2002 Apr 23;105(16):1887-9

89. Spragg D et al. Complications of catheter ablation for atrial fibrillation: Incidence and predictors. *Journal Cardiovascular Electrophysiology*. 2008;19:627-631.
90. Stollberger C, Schneider B, Finsterer J. Elimination of the left atrial appendage to prevent stroke or embolism? Anatomic, physiologic, and pathophysologic conderations. *Chest* 2003 Dec;124(6):2356-62. Review.
91. Stuart J. Connolly, Janice Pogue, John Eikelboom, Gregory Flaker, Patrick Commerford, Maria Grazia Franzosi, Jeffrey S. Healey, Salim Yusuf and on behalf of the ACTIVE W Investigators. Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range. Circulation 2008;118;2029-2037; originally published online Oct 27, 2008
92. Takahashi N, Akira S, Imataka K, Fujii J. Clinical features of paroxysmal atrial fibrillation. An observeation of 94 subjects. Jpn Heart J. 1981 March 22(2);143-49.
93. The effect of low-dose warfarin on the risk of stroke in subjects with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med*. 1990 Nov 29;323(22):1505-11. (Abstract only)
94. Transient Ischemic Attack – Proposal for a New Definition. TIA working group. *N Engl J Med*, Vol. 347, No. 21 · November 21, 2002
95. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010 Apr 15;362(15):1363-73.
96. Van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs Aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis; *JAMA*. 2002 Nov 20;288(19):2441-8.
97. Vural A, Agacdiken A, Ural D, Sahin T, Kozdag G, Kahraman G, Ural F, Akbas H, Suzer K, Komsuoglu B. Effects of cardiac resynchronization therapy on left atrial appendage function and pulmonary venous flow pattern. *Int J Cardiol*. 2005 Jun 22;10(1):103-9.
98. Walsh K, et al. Left Atrial Appendage Closure With the AMPLATZER Cardiac Plug: Results of the European Prospective Observational Study. Paper presented at: EuroPCR, 2012 May 15-18; Paris.

2.31 DEFINITIONS

Atrial Fibrillation (AF) – Rapid, incomplete, disorganized activity of the upper chambers of the heart (atria) resulting in rapid, irregular, and uncoordinated movement. On ECG, characterized by rapid baseline oscillations that vary in size, shape, and timing, usually recognized as having rates greater than 320 beats per minute.

Paroxysmal AF –Characterized as episodes of self-terminating, atrial fibrillation that generally last seven days or less (usually less than 24 hours); may be recurrent

Persistent AF –Refers to subjects in whom the AF episodes were not self terminating and last greater than seven days *or lasts less than seven days if they required cardioversion*

Permanent AF - Permanent AF is defined as a condition in which sinus rhythm cannot be sustained for seven days after cardioversion or the patient and physician have decided against further efforts to restore sinus rhythm. It includes cases of long-standing AF (e.g., greater than one year)

Audit – A systematic and independent examination of study-related activities documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, Sponsor's standard operating procedures (SOPs), and applicable regulatory requirements.

Budget – The amount of money designated by the Sponsor for conducting the clinical trial.

Case report form (CRF) – A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

$CHADS_2$ Risk Criteria

Prior stroke or TIA (defined as stroke or TIA occurring prior to the first documented onset of AF by the physician. Subjects diagnosed with stroke or TIA on the same day as diagnosing AF must be excluded from the CHADS2 assessment)

- Age greater than 75 years
- Hypertension with (with a systolic BP of $>$ 160mmHg at the time of screening)
- Diabetes Mellitus (defined by history of a fasting glucose of at least 140mg/dl or a random glucose of at least 200mcg/dl, or use of insulin or hypoglycemic medications)
- Heart Failure (recent CHF or LVEF less than or equal to 35%)

Clinical study – A study to evaluate a product using human subjects, in the treatment, prevention, or diagnosis of a disease or condition, as determined by the product's benefits relative to its risks.

Confidentiality – Prevention of disclosure to other than authorized individuals, of a Sponsor's proprietary information or a subject's identity and medical information.

Contract – A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters.

Diabetes mellitus – History of a fasting glucose of at least 140mg/dl or a random glucose of at least 200mg/dl, or use of insulin or hypoglycemic medications.

Edit Logic – Programmed rules (in the form of edit checks) applied to a study database to catch any unexpected errors on CRFs. A DCF can be automatically generated when the logic of the edit check is met.

Good clinical practice – A standard established by the International Conference on Harmonization (ICH) for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical studies that provides assurance the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of study subjects are protected.

Hemorrhagic Stroke-acute focal neurological deficit presumed to be due to focal ischemia, with either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct with hemorrhagic conversion

Institutional review board (IRB) – An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a research study by, among other things, reviewing, approving, and providing continuing review of studies, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the study subjects.

Investigational medical device – A medical device (including an in vitro diagnostic device) being tested or used in a clinical trial, including a product with a marketing authorization when used or assembled in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator – An individual who conducts a clinical investigation, under whose immediate direction the test article is administered, dispensed to, or used involving a subject; or in the event of an investigation's conduct by a team of individuals, is the responsible leader of the team.

Ischemic Stroke acute focal neurological deficit presumed to be due to focal ischemia, with either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct

Legally authorized representative – An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the procedures(s) involved in the research.

Monitoring – The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, and applicable regulatory requirement(s).

NYHA Functional Classification

- Class I: No symptoms and no limitation in ordinary physical activity

- Class II: Mild symptoms and slight limitation during ordinary activity Comfortable at rest
- Class III: Marked limitation in activity due to symptoms even during less than ordinary activity. Comfortable only at rest
- Class IV: Severe limitations. Experiences symptoms even while at rest

Oral Anticoagulation (OAC) – A class of drugs that prevents coagulation of blood. Within this investigational protocol, OAC refers to warfarin and/or dabigatran.

Optimal Medical Therapy (OMT) – Within this investigational protocol, OMT refers to warfarin or dabigatran with or without concomitant aspirin. This is determined for each subject by the investigator at baseline. This does not include rivaroxaban which is excluded in this trial.

Peripheral Thromboembolism - An abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism

Protocol Deviation – A deviation from the investigational plan

Quality assurance – All planned and systematic actions established to ensure the study is performed and data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

Screening – The process of evaluating potential clinical trial subjects to determine if they meet protocol eligibility criteria before enrolment.

Study close-out visit – The final visit made to a site after the study has been completed or terminated.

Subject – An individual who participates in a clinical trial, either as a recipient of the investigational drug or medical device, or as a control. The terms subject and participant are used synonymously.

Subject identification code – A unique identifier assigned by the investigator or the Sponsor to each study subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other study-related data.

Sustained discontinuation of warfarin or dabigatran- The subject's ability to remain off of warfarin or dabigatran for a minimum of 6 months following discontinuation of warfarin or dabigatran except in subjects with less than 6 months of follow-up. 'Sustained discontinuation' for those subjects who have less than 6 months of follow-up is defined as the subject's ability to remain off of warfarin or dabigatran for a minimum of 3 months following discontinuation of warfarin or dabigatran.

Transient Ischemic Attack acute focal neurological deficit (such as focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit) presumed due to focal ischemia, with symptoms persisting greater than or

equal to 5 minutes and less than 24 hours, that is not associated with MR or CT findings of a new cerebral infarct

3. RISK ANALYSIS

3.1 RISK: BENEFIT ASSESSMENT OF THE DEVICE ARM

3.1.1 Risks Associated With the Procedure

The risks associated with the ACP procedure are similar to those of other cardiac catheterization procedures. Some of the potential risks associated with the procedure may include, allergic reactions during the procedure to contrast, drugs, products (latex), or anesthesia; adverse events related to vascular access; and/or adverse events related to catheter manipulation. Other adverse events associated with cardiac catheterizations may include, but are not limited to the following; arrhythmia, brachial plexus injury, cardiac arrest, cardiac tamponade, fever, infection, kidney damage, myocardial ischemia/infarction, pericardial effusion, and death. Refer to Section 2.13.2 for a complete list of anticipated adverse events.

Radiation risks associated with the procedure will be comparable to a diagnostic catheterization procedure.

3.1.2 Product Risks

The risks associated with ACP are similar to other implantable cardiac occlusion devices. Some of the potential risks include but are not limited to those listed below:

- Device Embolization
  Device embolization may occur if an improper device size is used or the device is incorrectly seated. If the device embolizes prior to release, it can be partially pulled inside the delivery catheter for repositioning. If the device embolizes after release, it should be removed as soon as possible; surgery may be necessary.

- Bacterial Endocarditis
  The ACP is a foreign body which will be permanently implanted and therefore subjects are at risk of bacterial endocarditis. Bacterial endocarditis may contribute to heart failure, arrhythmias, damage to the heart muscle and blood clots. If left untreated, bacterial endocarditis can lead to death.

- Device Thrombus
  Thrombus formation on the device could potentially result in subsequent embolization, infectious endocarditis, arrhythmias, stroke/TIA, or death.

- Pericardial Effusion
  ACP may perforate the visceral pericardium and lead to accumulation of fluid in the pericardial cavity which may result in cardiac tamponade.

- Cardiac Tamponade
  If pericardial effusion becomes sufficiently large, cardiac contractility maybe compromised leading to low cardiac output and possibly cardiogenic shock or death.

- Allergic device reaction
  Idiosyncratic reaction to the device implanted.

- Nickel sensitization
  Alteration of the responsiveness of the body to nickel

- Carcinogenicity
  Potential carcinogenicity risk. The ACP device consists of a nickel-titanium alloy. In vitro testing has demonstrated that that nickel is released from this device for a minimum of 60 days. Some forms of nickel have also been associated with carcinogenicity (ability to cause cancer) in animal models. In humans, carcinogenicity has been demonstrated only through an inhalation route (breathing nickel in), which will not occur with this procedure.

3.1.3 Potential Benefits

The primary potential benefit is that the subjects may not need to be on long-term warfarin or dabigatran therapy and thus will not be exposed to its associated complications. In addition, the ACP will be implanted via transcatheter approach. Subjects who receive the device may also decrease the associated risk of thromboembolism.

3.2 RISK: BENEFIT ASSESSMENT OF THE CONTROL ARM

3.2.1 Risks Associated With Warfarin

Warfarin therapy requires continuous monitoring and dose management to optimize therapy and avoid associated adverse events. The anticoagulant effect of warfarin is influenced by concomitant use of antiplatelet agents. Furthermore, many other medications, as well as diet, interfere with the metabolism of warfarin, either potentiating or inhibiting its anticoagulant effects.

Warfarin levels which are either too high or too low have associated risks. Subtherapeutic levels do not lessen the risk of thromboembolic events. Levels which are too high may result in bleeding. The bleeding risk appears higher in subjects with a history of prior stroke or gastrointestinal bleeding. Another important, but uncommon adverse effect of warfarin is skin necrosis.

Warfarin is associated with a 2.2% increased risk of major fatal or nonfatal bleeding, and 7.7% increase in minor hemorrhagic complications per year (Gullov 1994).

3.2.2 Risks Associated With Dabigatran

Dabigatran increases the risk of bleeding and can cause significant and sometimes fatal bleeding. Risk factors for bleeding include the use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of Non-steroidal anti-inflammatory drugs (NSAIDs)).

Dabigatran's anticoagulant activity and half-life are increased in subjects with renal impairment.

A specific reversal agent for dabigatran is not available.

3.2.3 Risks of Concomitant Use of OACs and Aspirin

Cardiovascular professional society guidelines recommending concomitant aspirin usage with OACs vary based on targeted patient population and/or disease type to be treated. Current professional society guidelines for use of concomitant aspirin with oral anticoagulation / antiplatelet therapy for subjects likely to be treated under this clinical protocol are summarized in the table below.

Summary of Professional Guidelines and Concomitant Aspirin Usage

Guideline*	Recommendation
ACC/AHA/SCAI 2007 Guideline Update for Percutaneous Coronary Intervention	In pts. requiring warfarin, clopidogrel, and aspirin after PCI, target INR of 2.0–2.5 is recommended with low-dose aspirin (75–81 mg) and a 75-mg dose of clopidogrel
ACC/AHA 2007 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction	If indication for anticoagulation, add warfarin (INR 2.0–3.0) to aspirin
AHA/ASA 2006 Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack	Warfarin (INR 2.0–3.0) + aspirin <162 mg daily
ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction	Low-dose aspirin 75–81 mg daily + warfarin (INR 2.0–2.5)
2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC: 2006 Guidelines for the Management of Patients with Atrial Fibrillation	When warfarin is given in combination with clopidogrel or low-dose aspirin, dose intensity must be carefully regulated
AHA/ACC Guidelines for Secondary Prevention for Patients with Other Atherosclerotic Vascular Disease: 2006 Update: Endorsed by the National Heart, Lung, and Blood Institute	Add warfarin (INR 2.0–3.0) when clinically indicated

**Note: this table is a representative sample of guidelines as of the date of this protocol revision (Revision 06, August 2012). Please refer to current professional guidelines for the most recent updates.*

Despite the recommendations above, aspirin may offer only modest protection against stroke for patients with atrial fibrillation (Fuster 2011), thus the clinical utility of aspirin use in non-valvular atrial fibrillation is an area of uncertainty. The risk of concomitant use of oral anticoagulants and aspirin may be associated with an increase in bleeding risk. As such, the concomitant use of OACs and aspirin is considered a matter of clinical judgment by the treating physician understanding that the potential benefits of continued aspirin outweigh the potential bleeding risks.

It is further recommended that when warfarin is given in combination with low-dose aspirin, the dose intensity must be carefully monitored. For further information refer to the package insert for warfarin (Coumadin® product insert, Bristol-Myers Squibb, 293US11PBS01503).

Based on available published literature, i.e. RE-LY trial (Connolly et al 2009), the concomitant use of aspirin with dabigatran in non valvular AF patients resulted in an annual stroke and systemic embolism rate of 1.07% but may also be associated with increased risk I bleeding. This included 20-30% of patients taking concomitant aspirin with dabigatran. There may also be an associated risk of increased bleeding. Among patients receiving concomitant aspirin or clopidogrel in RE-LY, an increased risk of major bleeding was observed (HR 1.76, 95% CI 1.55–2.00), which was similar for dabigatran 110 mg, 150 mg or warfarin (Dans 2011). Therefore, similar caution is recommended for treating physicians considering co-administration of dabigatran with other anticoagulants or antiplatelet agents.

3.2.4 Potential Benefit

The potential benefit is that the information obtained from this study may change future treatment of subjects with nonvalvular AF.

3.3 MINIMIZING THE RISKS

To minimize potential clinical risks to subjects participating in this clinical trial:

- This study will undergo a review and approval process to be monitored by investigational site Institutional Review Boards (IRBs). The IRBs will also review all study-related documents such as the protocol, participant recruitment announcements, and consent forms.
- The FDA will also review the protocol and consent forms.
- Investigators will be carefully selected based on their knowledge of, and experience treating AF.
- Investigators will be trained with regards to implantation technique of the ACP.
- Investigators will be provided with detailed Instructions For Use as a reference.
- The DSMB and/or CEC will have oversight throughout the clinical trial.

- The Steering Committee will act as an advisory board for the pivotal phase.
- Investigators will be required to follow The American Heart Association recommendations for endocarditis prophylaxis during the clinical trial; and
- Investigators or designated personnel administering the NIH Stroke Scale questionnaire will be certified.

In addition, to reduce the risks of specific device related adverse events:

- The subject eligibility criteria include minimum and maximum LAA dimensions to be treated with the ACP, which should minimize the risk of device embolization, device migration and perforation; and
- Subjects will be administered Heparin during the procedure and OMT therapy after the procedure; once warfarin/dabigatran therapy is discontinued, 325mg of aspirin will begin.

4. DESCRIPTION OF DEVICE

The AMPLATZER Cardiac Plug (ACP) is a transcatheter self-expanding device constructed from a nitinol mesh and polyester patch. ACP consists of a lobe and a disc connected by a central waist. The ACP is available in 8 diameters sizes, 16, 18, 20, 22, 24, 26, 28, and 30 mm. The device is designed to prevent thrombus embolization from the left atrial appendage (LAA) in subjects who have nonvalvular atrial fibrillation. The lobe has stabilizing wires to improve device placement and retention. The device has threaded screw attachments at each end for connection to the delivery and loading cable as well as radiopaque markers at each end and at the stabilizing wires.

Order number	Lobe diameter (mm)	Disc diameter (mm)	Length of the lobe
9-ACP-IDE-016	16 mm	20 mm	6.5mm
9-ACP-IDE-018	18 mm	22 mm	6.5mm
9-ACP-IDE-020	20 mm	24 mm	6.5mm
9-ACP-IDE-022	22 mm	26 mm	6.5mm
9-ACP-IDE-024	24 mm	28 mm	6.5mm
9-ACP-IDE-026	26 mm	30 mm	6.5mm
9-ACP-IDE-028	28 mm	32 mm	6.5mm
9-ACP-IDE-030	30 mm	34 mm	6.5mm

The AMPLATZER TorqVue Delivery Systems consists of a Delivery Sheath and Dilator.

<table>
<tr><th>AMPLATZER Cardiac Plug</th><th>Compatible AMPLATZER TorqVue Delivery Systems</th></tr>
<tr><td>9-ACP-IDE-016</td><td>9-TV45x45-9F
9-TV-LA1-9F
9-TV-LA2-9F</td></tr>
<tr><td>9-ACP-IDE-018</td><td rowspan="3">9-TV45x45-10F
9-TV-LA1-10F
9-TV-LA2-10F</td></tr>
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<tr><td>9-ACP-IDE-022</td></tr>
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9-TV-LA1-13F
9-TV-LA2-13F</td></tr>
<tr><td>9-ACP-IDE-026</td></tr>
<tr><td>9-ACP-IDE-028</td></tr>
<tr><td>9-ACP-IDE-030</td></tr>
</table>

5. MONITORING PROCEDURES

As indicated by the guidelines established for Investigational Device Exemptions by the FDA (21 CFR 812). AGA Medical will comply with external and internal monitoring requirements, including development of a monitoring plan, for this investigational study. Monitoring will be conducted by AGA Medical clinical personnel; overall monitoring oversight is the responsibility of Clinical Monitoring Manager.

6. SAMPLE SUBJECT IDENTIFICATION CARDS

All study participants are provided with a Subject Identification/Follow up Card regardless of the randomization assignment.

SAMPLE PATIENT ID/FOLLOW-UP CARD

AMPLATZER™ Cardiac Plug Clinical Trial
Patient Identification Card

The holder of this card is participating in the AMPLATZER Cardiac Plug (ACP) Clinical Trial sponsored by AGA Medical (St. Jude Medical)

Patient Initials :	ABC
Trial ID Number:	123-ACP-456
Enrollment Date: (mm-dd-yyyy)	01-01-2010
Hospital/Clinic:	Heart Hospital USA
Doctor Name:	John Doe, MD
Doctor Phone:	(555)-555-5555

Front of

AMPLATZER™ Cardiac Plug Clinical Trial
Follow-up Schedule

Trial Visit	Scheduling Window (mm-dd-yyyy)
45 days	(02-10-2010 - 02-20-2010)
6 month	(05-31-2010 - 07-30-2010)
12 month	(12-02-2010 - 01-31-2011)
18 month	(05-01-2011 - 08-29-2011)
2 year	(11-02-2011 - 03-01-2012)
3 year	(11-01-2012 - 03-01-2013)
4 year	(11-01-2013 - 03-01-2014)
5 year	(11-01-2014 - 03-01-2015)

AGA Medical (St. Jude Medical)
1-888-546-4407 www.sjm.com

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SAMPLE DEVICE ID CARD

Only subjects who receive an ACP device receive the card below.

AMPLATZER™ Cardiac Plug Clinical Trial
Device Identification Card

Patient Initials:
Trial ID Number:

Hospital/Clinic:
Doctor Name:
Doctor Phone:

Implant Date:
(mm-dd-yyyy)

Product Name:
Product Number:
Lot Number:
Serial Number:

Front of

The carrier of this card has been treated with an implantable device and is in a clinical trial. The study (investigational) device is NON-FERROMAGNETIC / MR conditional and can be scanned safely under the following conditions:

MR

- Static magnetic field of 3.0 Tesla or less
- Spatial gradient field less than or equal to 30 T/m
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning

Notify your doctor if there is a change in your medical condition or address.

If you experience shortness of breath or chest pain:
- Seek medical attention immediately
- An echocardiogram may be required

If a stroke or TIA (mini-stroke) is suspected:
- Seek medical attention immediately
- A brain MRI must be performed within 10 days of the event as part of the trial.
- A brain CT scan should be performed instead of a MRI if a MRI is contraindicated (medical reason not to perform)

Manufactured by: AGA Medical (St. Jude Medical), 5050 Nathan Lane N Plymouth, MN 55442 (U.S.A.) Phone 1-888-546-4407 / www.sjm.com

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7. CONSENT MATERIALS

Informed Consent Template
AMPLATZER™ Cardiac Plug (ACP) Clinical Study

Patient Consent Form authorizing participation in a clinical research trial with assignment to either treatment with the device under clinical investigation, or warfarin or dabigatran (current standard of care) in patients with non-valvular atrial fibrillation.

Participant's Name:

Date:

You are being asked to read this form so that you understand the nature of this clinical study and how you might take part in it. Signing this form will show that you understand and that you agree to take part in this clinical study. Written informed consent is required before you can take part in this clinical research study.

Why am I being asked to read this form?

You are being asked to take part in this study because your doctor has told you that you have or have had an abnormal heart rhythm called atrial fibrillation (AF). Normally electrical signals from the upper chambers of the heart (atria) travel through to the lower chambers of the heart (ventricles) and cause them to beat in a very regular way. During AF, the electrical signals in your heart are abnormal, and cause the upper chambers of the heart (atria) to beat too fast and irregularly.

This irregular beating of the heart leads to slowing of the blood in the upper chambers. In the left upper chamber there is a small pouch called the left atrial appendage (LAA). Slowing of blood, especially in the LAA, may cause blood clots to form. The clots may move from the LAA and travel to the brain, causing a stroke or transient ischemic attack (TIA), also called a mini-stroke. These blood clots may also travel to other parts of the body and block blood vessels. This clinical research study is designed to evaluate a new device the AMPLATZER Cardiac Plug (ACP) to close your LAA which may decrease the chance of a new blood clot forming and moving from the LAA.

Your doctor has given you this form to tell you about this research study and to ask whether you are willing to participate in this study. If given, your consent to join this study will be documented by your signature on the last page of this form only after you fully understand the study. Your participation is voluntary. You will also be able to ask questions before you agree to be in this study.

Why is this study being done?

The purpose of this research is to evaluate the safety and effectiveness of the AMPLATZER Cardiac Plug. This will be done by comparing the results of this device to standard therapy with the medicines warfarin or dabigatran. Warfarin (Coumadin®) and dabigatran (Pradaxa®) are

medicines that help to thin your blood and prevent blood clots from forming. These are common medications given to people who have AF.

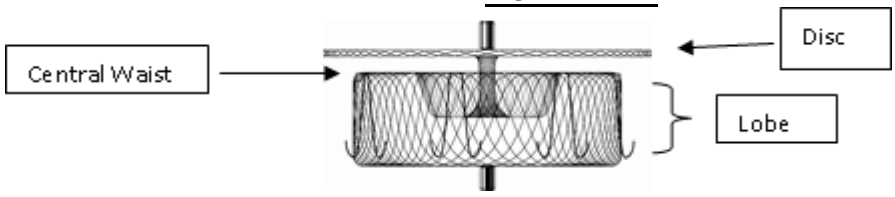
Who is the study Sponsor?

AGA Medical LLC, a U.S. medical device company is the Sponsor of this study and will be providing financial support for this clinical study. The principal investigator and co-investigator(s) in this study are also healthcare providers. They are interested in the knowledge to be gained from this study and in your well-being. The health care facility and investigators will receive financial support for conducting the research.

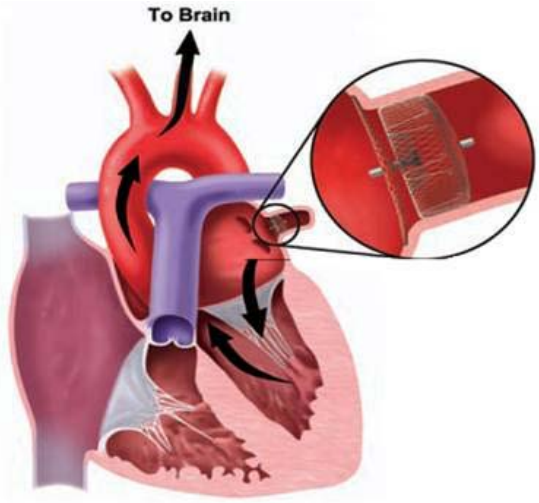
What is the study device?

The AMPLATZER Cardiac Plug (ACP) is a self-expanding device which is made from a nitinol (nickel-titanium alloy) mesh and which has a lobe and a disc connected by a central waist. The device is designed to prevent blood clots from moving out of the left atrial appendage (LAA). The lobe has small stabilizing wires that help keep the device in place. The device has fabric sewn into the disc and the lobe. This polyester material is the same as that used in other heart devices and by surgeons to repair heart problems. The fabric helps stop the flow of blood into the LAA. The device has screw attachments at each end so it can be placed in the heart. The study device sizes range from 16 mm to 30 mm. This device is investigational which means it has not been approved by the FDA for commercial use in the United States.

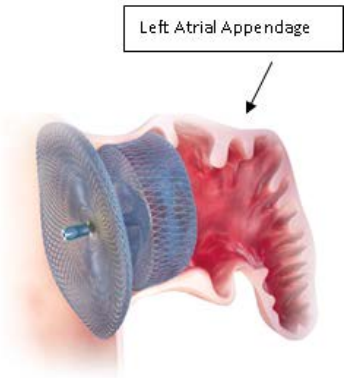
ACP Device



Device implanted heart



Device in left atrial appendage



How long will I be in the study?
Your total study participation is expected to last about 5 years.

About how many participants will be in the study?
The study will include up a minimum of 400 and maximum of 3000 participants at a maximum of 80 sites in the United States and up to 10 sites in Canada. An initial safety study was conducted in 2010-2011 which enrolled 45 subjects and now the study is continuing and expanding.

What tests, procedures and treatments will I have as part of the study?
If you decide to participate, you will have medical tests to see if you qualify to be part of the study. During your participation in the study, you may have more medical tests and/or procedures. Some tests may be done more than once.

Study-Specified Tests/Procedures

Baseline Testing
You will have the following tests once you sign this form and agree to be in this study. These are common tests for someone with atrial fibrillation and might be performed even if you do not join this study. You should be aware that some of the tests performed may need to be repeated. You will have a physical exam and be asked questions about your medical and medication history.

Blood tests will be performed to test for abnormal clotting factors and some additional standardized blood tests. A needle will be placed in a vein in your arm or hand and about 10-12 ml (approximately 2-3 teaspoons) of blood will be drawn. Some of this blood testing will be sent to an outside lab for testing. If your study doctor indicates you should be taking warfarin, you will need to undergo regular blood tests called the International Normalized Ratio (INR). This will occur at the time of starting this study and then every month (four weeks) to make

sure your warfarin dose is correct. The amount of blood drawn may be a few drops to about 2-3 teaspoons each time.

Electrocardiogram (**ECG/EKG**) is a type of test that uses small electrodes placed on your body with a gentle adhesive. The electrodes pick up the electronic signals of your heart and translate them into a report that helps your doctor understand your heart rhythms.

Magnetic resonance imaging (**MRI**) uses a powerful magnetic field to produce detailed pictures of organs, tissues, bone and other body parts. For this study, a MRI of your head (brain) will be performed. You will lie on a table that moves into a large tube so that a large magnet can pass over your body.

Computed Tomography (CT) Scan is a type of x-ray that provides detailed pictures of body parts. For this study, a CT of your head will only be done if you are not able to have a MRI of your head performed due to medical conditions.

Pregnancy test for all women of childbearing potential will require a urine and/or blood sample. Women who are pregnant or plan to become pregnant throughout the duration of the study should not enter the study. If you suspect that you have become pregnant during the study, please inform the study coordinator or doctor immediately.

Transesophageal echocardiogram (**TEE**) is a type of echocardiogram (also called an echo), which is an ultrasound test that allows your doctor to look at the chambers of your heart using sound waves. You will receive medicine that will make you sleep (sedation). During this test, a small imaging probe is placed into your mouth and down your esophagus (your swallowing tube) in order to take pictures of your heart that may be seen on a video screen. Your throat may be a little sore for about one week after the test.

National Institute of Health Stroke Scale (NIHSS) is a set of questions that provides information about how your brain and nerves are working, especially at the time of or after a stroke.

Modified Rankin Scale is a score which measures the general level of functioning, especially after having a stroke.

$CHADS_2$ assessment is set of questions used to assess the level of risk of a future stroke in patients with atrial fibrillation.

Physical Exam is an evaluation of the body to determine state of health.

Quality of Life Assessment is a set of questions asking about your general health, wellbeing, and if you are able to do your usual activities. This data can be used to compare the two treatment groups.

Randomization

If after baseline testing and exams you meet all study requirements, you will be randomly assigned to one of two different study groups (the device group or the medicine group). Randomization is the process by which chance is used to assign you to a group (like pulling numbers out of a hat). In this study, you have twice as much chance of being assigned to the device arm as you do to the medicine group. Once you have signed this form and been assigned to a group, you will be officially enrolled in this study. You may not switch groups once assigned so you should be comfortable with the decision to go into either group if you want to participate in this study.

Medicine Group

If you are randomly assigned to the medicine group, you will continue to take either warfarin or dabigatran also called an oral anticoagulant (medicine used to "thin" your blood). Your doctor will decide the type and amount of medicine that is the best for you. If you take warfarin, blood samples (approximately 2-3 teaspoons or a finger prick) will be taken at a minimum of every month (four weeks) to make sure the right dose of medicine is being given to you. It is important to follow your doctor's instructions while taking blood thinning drugs. You will not have the ACP device implanted in your heart if you are assigned to the medicine group. In addition, your doctor may also have you take low dose aspirin (81 mg/day) with warfarin or dabigatran. Carefully follow your doctor's instructions on these medications. Immediately inform your study doctor any changes in the blood thinning medications you are taking.

Device Group

If you are randomly assigned to the device group, within 14 days of your randomization, the ACP device will be implanted (placed) in your heart to close your LAA. The ACP device will permanently remain in your heart.

Pre-Procedure Medication Change

If you are assigned to the device group and taking warfarin, you will stop taking warfarin four days before the implant procedure. Your doctor will have you start a new medicine called Lovenox (enoxaparin) two days before the procedure. Lovenox is another type of blood thinning medicine you will take by way of shots (injections). On the day of procedure, you will stop taking Lovenox. This change in medicine is required so that your blood is not too thin during the implant. You will have a blood test within 24 hours prior to the implant. If your blood is too thin, your implant procedure may need to be re-scheduled. Your doctor will provide you with more details about this process.

Example: Day 5 is day of procedure:

- Day 1 – stop warfarin
- Day 2 – no medications (Lovenox or warfarin)
- Day 3 – begin Lovenox
- Day 4 – continue Lovenox
- Day 5 - procedure day, no Lovenox (or warfarin)

If you are assigned to the device group and taking dabigatran, you will stop dabigatran prior to your implant. Your doctor will provide you with more details about this process

Implant Procedure

The implant procedure will occur in the cardiac catheterization laboratory, or "cath lab". Conscious sedation (medicine that will make you relaxed and sleepy yet awake) or general anesthesia (medicine that will make you sleep) will be used. This is a non-surgical procedure done using an angiogram in which a catheter is put into a blood vessel in your groin and up into your heart. An angiogram is a test using x-rays where a liquid (contrast) is injected into a blood vessel which allows your doctor to view pictures of your heart and blood flow. A catheter is a sterile, flexible, hollow tube that is put into a blood vessel to let fluids go into or out of your body, or to deliver devices to your heart. After the procedure, you may have some minor pain in the groin area where the catheter was inserted.

To help your doctor evaluate your LAA during the procedure, you will also have a transesophagael echocardiogram (TEE). If a blood clot is found in your heart, your doctor will not proceed with device placement. If no blood clot is found in your heart, then your doctor will take measurements of your LAA. The doctor will make a small puncture through the septum, muscular tissue that separates the two sides of the upper heart, in order to gain entry into the upper left heart chamber. An appropriate size ACP device will be passed through the catheter and placed in your LAA. After your doctor is satisfied with the position of the device and catheter are removed. The procedure will take about 1-2 hours. The device will remain in your heart. Over time, the tissue in your body will cover and grow around the device to further secure (hold) the device in place. If your doctor is unable to place a device you will still come in for follow-up visits for the remainder of the trial.

After the Procedure

After the procedure but before you are discharged from the hospital, you will undergo a follow-up visit which will include a physical exam, ECG, and a transthoracic echocardiogram (TTE). A TTE is another type of echocardiogram that uses high-pitched sound waves that are sent through a transducer (hand-held plastic instrument which looks like a microphone) which is placed on different areas of your chest. The transducer picks up echoes of the sound waves as they bounce off the different parts of your heart and turns them into moving pictures of your heart that can be seen on a video screen. A TTE is done to verify the position of the device in your heart and to check for any potential complications after the implant. You will be asked to continue to take warfarin or dabigatran after the implant.

If you are taking warfarin, you will have INR blood tests to ensure that you are taking the correct amount of medicine. In addition to warfarin, you may also take Lovenox for a short time until your INR is in the correct range. If you are taking dabigatran, follow your doctor's orders on when to start taking the medicine after you leave the hospital.

To prevent certain bacterial infections, you may need to take an antibiotic medication during the first 6 months following the placement of the device, especially if you are planning to undergo

procedures such as dental cleanings. Your doctor may have you continue to receive antibiotics for certain procedures.

If you need to have a MRI scan after the implant, it is safe to do under certain conditions. Let your doctor or the technician know that you have an implanted device and show your patient identification card (device ID card). Also, your ACP device will not set off alarms when going through airport security.

Health Economic Sub-study

The Sponsor is also conducting a health economic sub-study. This sub-study will evaluate the costs and benefits of treatment. This information is being collected so the Sponsor can understand the cost effects of the treatment in the ACP study. During the health economic sub-study, information about your reported resource use and hospital bills reporting hospital care will be collected. This information about your hospital bills will be collected by the Sponsor's independent contractor who will perform the health economic sub-study. You will not be personally contacted by the Sponsor, the Investigator, or the independent contractor and asked to obtain your billing data for the purpose of providing it to the independent contractor for this research purpose. This resource use information and your hospital bills related to any hospitalization will be collected at least through 2 years and until the study is done. Medical resource use, cost and health-related quality of life within the trial period will be compared between study subjects in the medicine group and the device group.

Follow-up Visits and Testing

The ACP study requires both groups have follow-up visits at 45 days, 6 months, 12 months, 18 months, 2 years and every year after that until the study is done. If you receive a device and can stop taking warfarin or dabigatran per your echocardiogram results, you will have a phone follow up 3 months after you stop taking warfarin or dabigatran to check on your medications and general health.

Below is a chart listing the requirements for people in both the medicine and device groups.

	45 days	**3 months after stopping warfarin or dabigatran (phone visit)**	**6 months**	**12 months**	**18 months**	**2 years**	**Annually thereafter (phone visit)**
Physical exam	X		X	X	X	X	
Neurological Symptoms Interview	X		X	X	X	X	X
12 lead Electrocardiogram	X		X	X	X	X	
MRI of brain (or CT scan if medically indicated)				X		X	

Medication check (only people who receive the device and discontinue warfarin/dabigatran)		X					
Quality of Life Interview				X		X	
Hospital bills	X - Until completion of the study						

The neurological interview which takes place at each visit contains a series of eight short questions about whether you have had any symptoms of a stroke or TIA. Additional testing may be performed by your doctor if medically necessary.

If your doctor suspects you may have had a new stroke or TIA, you will have two neurologic assessments (NIHSS and Modified Rankin) and a MRI or CT of your head. The MRI or CT scan must be performed within 10 days of the onset of the new stroke or TIA. You may need to set up extra appointments to complete these tests. If a stroke is confirmed, subjects who received a device will also have a TEE.

If at any time you have symptoms of a stroke or TIA, you should call 911 or be seen immediately by a doctor. Symptoms of stroke or TIA may be one or more of the following:

- Sudden numbness or weakness on the face, arm, leg, especially on one side of the body
- Sudden confusion, trouble speaking or understanding
- Sudden trouble seeing in one or both eyes
- Sudden trouble waking, dizziness, loss of balance or coordinator
- Sudden, severe headache with no known cause

Let your study doctor know about any symptoms as soon as possible after you are evaluated or receive treatment or are in the hospital for any reason. Do not wait until your next scheduled visit to let the study team know what happened. Call your study doctor or have a family member do so if you go to the emergency room, are hospitalized, or have any procedures at a different medical center from where you see your study doctor. Make sure to inform all heath care professionals who treat you outside of the study that you are participating in a medical device trial.

As part of the research study, you will be periodically asked to complete a questionnaire on your general well-being (quality of life). This information allows the Sponsor to gather data which may impact future health care policy and health insurance coverage of new medical devices.

If your study doctor has prescribed warfarin, this study requires that at all times you are taking warfarin; you must have your INR tested every month (4 weeks) until the study is completed or until you are taken off warfarin. This includes in you are taking warfarin in the medicine group or are taking warfarin in the device group. These INR tests are to make sure that your INR is stable and that the warfarin dose you are taking is correct.

For people in the device group and who receive a device, you will have some additional echocardiograms or echoes. These are being done for a number of different reasons.

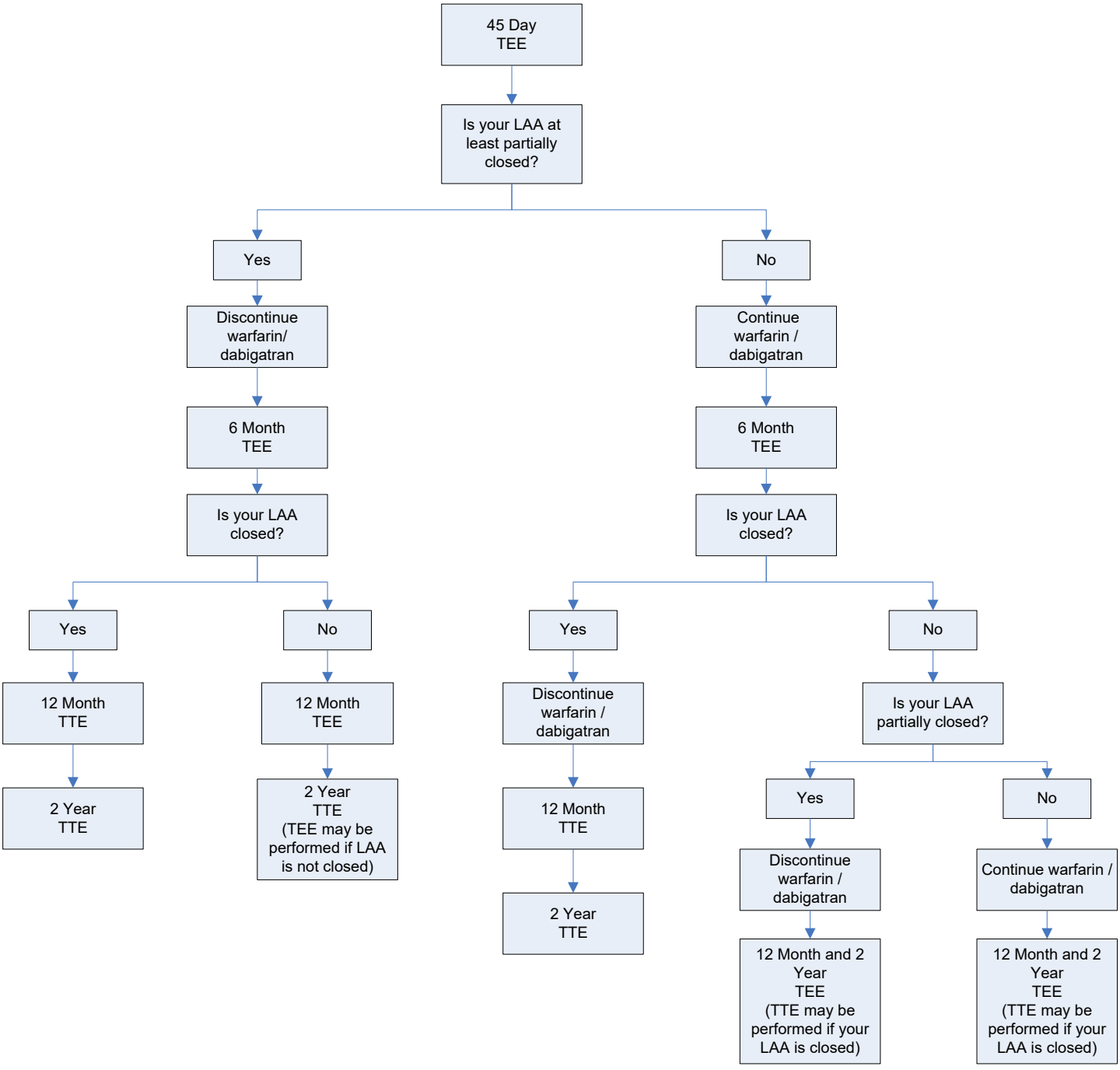
1) Your doctor will use this test to determine that the device is in the correct position, to see whether or not there are any clots on the device, and to look for any changes in your heart after the implant.

2) If your LAA is closed or partially closed (just a little blood flow is seen moving into or out of the left atrial appendage) you will be able to stop taking warfarin or dabigatran

3) Once your left atrial appendage is closed and depending on the visit, you may have a transthoracic echo (chest echo) instead of a transesophageal echo (swallowing tube echo).

The flow chart below shows the requirements for the type of echo you will receive if you are randomly assigned to the device group. The flow chart describes echo assessments starting at the 45 day follow-up visit through the remainder of the study and indicates whether or not you may be able to discontinue warfarin or dabigatran during the study.

Transesophageal Echo Schedule for Patients Randomly Assigned to the Device



Starting after the 2 year visit, your doctor may allow a phone follow-up to take place instead of an office visit.

During each visit, you will be asked about your health since your previous visit. You should report all changes in health to your doctor

It is important to keep all follow-up appointments scheduled for you. You will be given a card listing the times of when all visits should take place.

Are any of tests or procedures in this study experimental?

The AMPLATZER Cardiac Plug and implant procedure is considered by the United States Food and Drug Administration (FDA) to be an experimental.

What are the possible risks or discomforts of being in the study?

The risks associated with the implant procedure include, but are not limited to:

- Air embolus – leakage of air into the veins or heart
- Allergic reaction to contrast dye or medications used in the study
- Allergic reaction to the device implanted
- Anemia-a decrease in the number of red blood cells (RBC) or hemoglobin, resulting in a lower ability for the blood to carry oxygen to body tissues
- Anesthesia reaction
- Arrhythmia – abnormal heart beat
- Bacterial endocarditis – inflammation and infection of the heart
- Bleeding – loss of blood requiring blood transfusion
- Brachial plexus injury – injury to a group of nerves around the shoulder
- Bruising – blood leakage under the skin at the groin, catheter access site
- Cardiac arrest – failure of the heart to beat
- Cardiac perforation – tear or puncture of the heart wall caused by the guidewire or catheter
- Cardiac tamponade – a large amount of fluid in the sac which surrounds your heart and makes it difficult for the heart to beat strongly
- Congestive heart failure – failure of the heart to pump blood with normal efficiency
- Death
- Delivery system failure – the cable with the screw mechanism that the device is attached to when it is being placed in the heart does not work properly
- Device embolization – movement of a device from the intended location
- Device migration – movement of the device within the intended location
- Device thrombus – blood clot on the device
- Dyspepsia – upset stomach
- Erosion - rubbing of device against the heart wall or blood vessel and may lead to a tear or hole in the heart
- Fever – defined as body temperature greater than or equal to 101.5˚F
- Foreign body embolization – movement of device material, delivery system material, or other material from the intended location
- Gastrointestinal pain and/or bleeding – pain or bleeding from the any of the following areas; esophagus, stomach, small intestine, large intestine, rectum, and anus
- Hypertension – high blood pressure

- Hypotension – low blood pressure
- Hypoventilation – the state in which a reduced amount of air enters the lungs
- Infection – abnormal growth of germs in the body
- Myocardial infarction – a heart attack
- Myocardial ischemia – low blood flow to the heart
- Nickel sensitization – develop nickel allergy
- Perforation – tear or puncture of a blood vessel or organ
- Pericardial effusion – abnormal fluid collection around the heart
- Peripheral thromboembolism – blood clot anywhere in the blood vessels except in the heart and brain
- Pleural effusion – an abnormal collection of fluid around the lungs
- Renal failure – failure of kidneys to perform normal functions
- Respiratory failure – inability of the lungs to function
- Respiratory insufficiency – inability of the lungs to function normally
- Seizure – abnormal electrical activity in the brain, which may produce a physical convulsion
- Sepsis – the presence of bacteria or their poisonous products in the bloodstream
- Septicemia – body wide illness due to infection by bacteria
- Stroke – A sudden loss of brain function caused by a blockage or rupture of a blood vessel to the brain
- Systemic embolism – blood clot that travels through the circulation system and becomes stuck in an artery, blocking blood flow
- Thrombophlebitis – inflammation of a vein due to a blood clot
- Thrombus – a blood clot
- Tissue damage - damage to heart tissue
- Transient ischemic attack (mini stroke) – temporary interruption of blood flow to an area of the brain, causing symptoms like a stroke which last for less than 24 hours
- Valvular regurgitation/insufficiency – back flow of blood through any of the four heart valves
- Vascular access site injury – bleeding, discomfort, and/or bruising around the place where the catheter was put in the groin
- Vascular dissection - the process of cutting apart or separating blood vessel tissue

Potential risks when taking blood thinning medicines (wafarin, Lovenox, dabigatran, aspirin)

Reported risks associated with medicines used to thin the blood include, but are not limited to: increased bleeding time, bleeding from the stomach or bowels, bleeding in the brain, drowsiness, dizziness, headache, heartburn, stomach pain, loss of appetite, nausea, vomiting, and hives, rash, itching and bruising. Other risks include swelling of the eyes, face, lips, tongue, hands, feet, ankles, lower legs and throat, joint or muscle ache, wheezing or difficulty breathing, hoarseness, fast heartbeat, fast breathing, cold clammy skin, yellowing of the eyes

or skin, ringing in the ears or loss of hearing, difficulty swallowing, chest pain, fever, infection, diarrhea. If you are taking aspirin together with either warfarin or dabigatran, there is an increased risk of bleeding. Taking blood thinning medications can cause harm to an embryo, fetus or nursing infant. There may be other risks related to medicine used to thin the blood that are unknown at this time.

What other risks and discomforts might there be?

Risks involving nickel:

- This device is made up of a nickel-titanium alloy (mixture of metals), which is generally considered safe. However, lab testing shows that nickel is released from the implanted device for at least 120 days. Subjects who are allergic to nickel may have an allergic reaction to this device, especially those subjects with a history of reacting to metals such as jewelry, buttons, snaps, belt buckles, etc. Some allergic reactions can be serious; you should notify your doctor immediately if you have difficulty breathing or inflammation (reddening) of your face or throat.
- Some subjects may also develop an allergy to nickel if this device is implanted.
- Some forms of nickel have been associated with carcinogenicity (ability to cause cancer) in animal models. In humans, carcinogenicity has been demonstrated only through inhalation (breathing in nickel dust), which will not occur with this procedure.

If during the implant procedure (or post-implant) the device were to move out of position, the device may need to be removed by a catheterization procedure or surgically (open heart surgery). Cardiac surgery following device placement may be more difficult with additional risks.

There are also risks involved in the TEE. The most common risk of having a TEE is a sore throat; other possible risks include bleeding, breathing or heart problems, gagging, vomiting, pain when swallowing, dental injury, and damage or tear to your esophagus.

You may experience some brief and /or minor discomfort associated with drawing blood. For example, you may experience pain or bruising associated with the needle from the blood draw. Fainting and local infection can also occur although this is rare.

There is a risk of exposure to radiation during the x-ray procedures performed during the implant procedure (device subjects only). This risk is no different than any other standard cath lab procedure

There may be other risks that are unknown at this time. There may be unknown risks to an embryo, fetus or nursing infant if you become pregnant during this study.

What are the possible benefits of being in the study?

There may be no direct benefit to you for participating in this study. The information obtained from your participation may change the future treatment of people with atrial fibrillation.

Potential Benefits to the Device Group
The potential benefit is that the information obtained from this study may change future treatment of patients with atrial fibrillation.

Potential Benefits to the Medicine Group
The potential benefit is that the information obtained from this study may change future treatment of patients with atrial fibrillation.

What information can I show other health care professionals about this study?
You will receive a study participation and follow up card if you enroll in this trial. The card is the size of a plastic credit card and will contain information specific to your involvement in the study. The card lists when you were enrolled in the study and all time periods when you should return for study visits. Those participants assigned to the device group who have the device implanted, will also receive a device ID card with details on the implanted device.

Sample Patient ID/Follow-up Card (both groups will receive this)

AMPLATZER™ Cardiac Plug Clinical Trial
Patient Identification Card

The holder of this card is participating in the AMPLATZER Cardiac Plug (ACP) Clinical Trial sponsored by AGA Medical (St. Jude Medical)

Patient Initials :	ABC
Trial ID Number:	123-ACP-456
Enrollment Date: (mm-dd-yyyy)	01-01-2010
Hospital/Clinic:	Heart Hospital USA
Doctor Name:	John Doe, MD
Doctor Phone:	(555)-555-5555

Front of

AMPLATZER™ Cardiac Plug Clinical Trial
Follow-up Schedule

Trial Visit	Scheduling Window (mm-dd-yyyy)
45 days	(02-10-2010 - 02-20-2010)
6 month	(05-31-2010 - 07-30-2010)
12 month	(12-02-2010 - 01-31-2011)
18 month	(05-01-2011 - 08-29-2011)
2 year	(11-02-2011 - 03-01-2012)
3 year	(11-01-2012 - 03-01-2013)
4 year	(11-01-2013 - 03-01-2014)
5 year	(11-01-2014 - 03-01-2015)

AGA Medical (St. Jude Medical)
1-888-546-4407 www.sjm.com

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Sample Device ID Card (only people who have an ACP device implanted will receive this)

AMPLATZER™ Cardiac Plug Clinical Trial
Device Identification Card

Patient Initials:
Trial ID Number:

Hospital/Clinic:
Doctor Name:
Doctor Phone:

Implant Date:
(mm-dd-yyyy)

Product Name:
Product Number:
Lot Number:
Serial Number:

Front of

The carrier of this card has been treated with an implantable device and is in a clinical trial. The study (investigational) device is NON-FERROMAGNETIC / MR conditional and can be scanned safely under the following conditions:

- Static magnetic field of 3.0 Tesla or less
- Spatial gradient field less than or equal to 30 T/m
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning

Notify your doctor if there is a change in your medical condition or address.

If you experience shortness of breath or chest pain:
- Seek medical attention immediately
- An echocardiogram may be required

If a stroke or TIA (mini-stroke) is suspected:
- Seek medical attention immediately
- A brain MRI must be performed within 10 days of the event as part of the trial.
- A brain CT scan should be performed instead of a MRI if a MRI is contraindicated (medical reason not to perform)

Manufactured by: AGA Medical (St. Jude Medical), 5050 Nathan Lane N Plymouth, MN 55442 (U.S.A.) Phone 1-888-546-4407 / www.sjm.com

Back of

What other choices do I have if I choose not to be in the study?

If you choose not to participate in this study at this time, your doctor will discuss alternative treatments with you. Treatment options may include the use of drugs other than those planned for this study to prevent the occurrence of clots which can cause stroke, or not having any treatment at all.

Who will have access to my medical records?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate, by Sponsor (a U.S. company) and its affiliated companies (located in the U.S. and other countries), representatives designees of Sponsor that provide services related to the device and/or this study, Health Canada, the U.S. Food and Drug Administration, and the Research Ethics Board (REB) for the purpose of: 1) monitoring the research; 2) accurately document and report any adverse events that may occur during your participation in this study 3) satisfy any other requirements imposed by government authorities located throughout the world, including the U.S. FDA and Health Canada. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless otherwise permitted by law. Upon your approval, your regular doctor will be told of your participation in the study.

You will be assigned a unique study number as a subject by the Sponsor in this study. This number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the study investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

The Sponsor's independent contractor performing the health economic sub-study will receive a copy of your signed informed consent (which contains your name) so that they may contact your study doctor as well as hospital(s) to obtain copies of your medical bills. This information will be used as part of the health economic sub-study. Your personal health information obtained for this Study and the economic sub-study is confidential and will be treated as such to the extent required by law. No identifying information will be shared outside of the independent contractor and your care providers. This information is being collected so we can understand the cost effects of the treatment in the ACP study.

If you are hospitalized at a different facility that is not participating in this study or the sub-study, the non-study facility may not release your billing data without your permission. The independent contractor may work with the non-study facility to obtain this billing information. The non-study facility may require an additional review or ask you to provide a separate written permission in order to provider you billing information to the independent contractor. You will not be personally contacted by the Sponsor or the independent contractor and asked to obtain your billing data for the economic sub-study.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Because this is a study that also falls under U.S. regulation, in some circumstances the U.S. Food and Drug Administration (U.S. FDA) may seek to copy records that contain your personal information. If this occurs, you will be informed before the records are copied, but your consent may not be sought. You should be aware that privacy protections on personal information may differ in other countries.

Any study related data sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those dealing with protection of information may not be as strict as in Canada. However, all study related data that might be transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. By signing this consent form, you are consenting to the transfer of your information, to organizations located outside of Canada. Study related data collected about you will be coded and transferred to Sponsor (a U.S. company).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Will I receive payment if I am in the study?
You will not receive any payments for participating in this study.

What if I am injured during the study?
If you were to suffer harm of any kind as a direct result of this study, treatment for that injury including surgery, first aid, and emergency care will be available as needed. The hospital or clinic where you received treatment will bill your insurance company for the routine costs of care available under your health care plan and you may also have to pay some costs such as co-pays or deductibles.

If you followed all study instructions and are hurt during the study as a direct result of the study device or study procedures (not part of your routine medical care available under your health plan), AGA Medical will pay for reasonable and necessary medical and hospital expenses. This may include treatment(s) of a bad side effect affecting your health as a direct result of the study device that are not paid by your insurance company or other third parties.

AGA Medical will not cover the cost of injuries to the extent that they are caused by your failure to follow study instructions or other negligence, or that of the hospital or study doctor, the natural progression of an underlying condition (whether diagnosed or not) or pre-existing condition, or events that would have been expected from the standard treatment using currently approved therapies for your condition.

Signing this consent form in no way limits your legal rights against the Sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities.

Whom should I contact if I have questions or if I am injured during the study?
During the course of this clinical study, if you have any further questions, concerns, or research related injuries as a result of your participation, please contact ***[add Principal Investigator contact information here].***

For questions regarding your rights as a research subject, please contact the hospital ethics board (often called an IRB or Institutional Review Board) at ***[add IRB contact information here]***.

Can I refuse to participate in the study or stop participating once I am in the study?
Your participation in this research is VOLUNTARY. Your decision whether or not to participate will not affect your current or future relationship with your doctor or their institution. If you decide to participate, you are free to withdraw your consent and stop participation at any time. You will not be penalized or have any loss of benefits for deciding not to participate or for dropping out of the study. Information that has already been gathered before you leave the study may still be used and given to others as described in this form. If you decide to leave the study, you should tell your doctor so that appropriate continuation of care may be arranged for you.

What are the consequences if I decide to drop out of the study?
If you decide to drop out of the study, information about you will no longer be sent to the study Sponsor, and you may not have as many visits to your doctor and some tests may not be done. You will receive the same quality of care even if you decide not to stay in the study.

Can my participation in the study be stopped even if I don't ask to drop out?
Your doctor may stop your participation in this study if he/she believes it is best for you. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate. The study may also be stopped for administrative, medical, or other reasons as determined by AGA Medical LLC or the FDA, Health Canada and other applicable regulatory bodies. Again, information that has already been gathered before you leave the study may still be used and given to others as described in this form.

What if new information about the device is found during the study?
Any significant new information that develops during the course of the study that may affect your decision to participate will be provided to you. You may be asked to sign a new consent form with this new information.

What are the additional or anticipated costs to me if I am in the study?
Your health insurance (such as Medicare) will be billed for the routine costs that may be available under your plan that are associated with this study. You should check your insurance policy to know exactly what is included. If there are any co-payments or deductibles, you will be

responsible for making those payments. If you have any questions about your health insurance, or possible expenses, please talk with the study doctor and your health insurer or Medicare. The Sponsor cannot cover the costs that are part of your usual medical care and that would have been incurred regardless of your enrollment in the study. This includes but is not limited to warfarin (and INR testing), dabigatran, and aspirin as these drugs are considered standard treatment for people with AF.

What are my responsibilities if I am in the study?

As study participant, you are asked to follow study requirements, follow medical instructions given by your study doctor, inform your study doctor of any changes in your health, and inform your study doctor of any other medical care or drugs you are receiving (whether prescribed by a physician or bought over the counter).

By signing below I am indicating that:

- √ I have read and understood the patient/subject information of this study and the research staff has answered all of my questions regarding the study.
- √ I agree to participate in and comply with the requirements of this study
- √ I understand and agree that personal information about me will be collected from my medical records and processed by AGA Medical LLC or any other entity involved in the study.
- √ I authorize and instruct my physician(s) and the institution to release personal information about me necessary to conduct this study.
- √ I agree to tell my family I am in this study and let them know how to reach my study doctor if I am unable to do so myself.
- √ I agree to tell all medical care professionals who treat me outside of where I see my study doctor that I am in a research trial so all clinicians are well informed of my health and medicines I am taking.
- √ I understand that I may cancel my participation in this study at any time by telling the study coordinator or my doctor.

Subject Signature

Subject Signature _____ Date_____

Printed Name of Subject _____

Subject's Legal Representative (if necessary) Signature

Signature _____Date_____

Printed Name of Legal Representative_____

Person Conducting Informed Consent Discussion

Signature _____ Date _____

Printed Name _____

If you have questions concerning the rights of research subjects please contact:

_____
IRB

_____
Phone Number

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit {***add Investigator name here***} and staff members and AGA Medical LLC, the sponsor of the ACP clinical trial to use and disclose health information that identifies me for the purposes described below. I also agree to permit {***add hospital/clinical study site information here***}, my doctors, and my other health care providers to disclose health information in my medical records to the Researchers, AGA Medical LLC, and the FDA, Health Canada or other regulatory bodies for the purposes described below.

1. The health information that may be used and disclosed includes:
   - All information collected during the research as described in the Informed Consent Form, which includes my hospital bills and other health care resource use information; and
   - Health information in my medical records that is relevant to the research described in the Informed Consent Form.

2. The Researchers may:
   - Use and share my health information to conduct the research;
   - Disclose my health information to the Sponsor of research, AGA Medical Corporation and its affiliated companies (located in the U.S. and other countries), representatives designees that provide services related to the device and/or this study;
   - Disclose my hospital bills and information regarding my use of health care resources to Sponsor's independent contractor in order to conduct the health economic cost analysis related to this study;
   - Disclose my health information as required by law;
   - Disclose my health information to representatives of government organizations and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and
   - Remove from my health information my name and other information that could be used to identify me.

3. AGA Medical LLC and its affiliated companies (located in the U.S. and other countries), representatives designees that provide services related to the device and/or this study may;
   - Use and share my health information to conduct the research;
   - Disclose my health information as described in the Informed Consent
   - Disclose my health information as required by law;
   - Disclose my health information to representatives of government organizations and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and

- Remove from my health information my name and other information that could be used to identify me.

4. Once information that could be used to identify me has been removed, the information that remains is no longer subject to this Authorization and may be used and disclosed by the Researchers and AGA Medical LLC and its affiliated companies (located in the U.S. and other countries), representatives designees that provide services related to the device and/or this study as permitted by law.

5. Once my health information has been disclosed to a third party, privacy laws may no longer protect it from further disclosure. However, the Researchers and AGA Medical LLC agree to protect my health information by using and disclosing it only as permitted by me in this Authorization and the Informed Consent. Also, no publication about the research will reveal my identity without my specific written permission. These limitations continue even if I revoke (take back) this Authorization.

6. Please note that:
   - You do not have to sign this Authorization, but if you do not, you will not be allowed to participate in the research.
   - You may change your mind and revoke this authorization at any time. To revoke this Authorization, you must write to ***{name and contact information}***. However, if you revoke this Authorization, you will no longer be allowed to participate in the research. Also, if you revoke this Authorization, the information already obtained by the Researchers and AGA Medical LLC may be used and disclosed as permitted by the Authorization and the Informed Consent.
   - While the research is in progress, you will not be allowed to see your health information that is created or collected in the course of the research. After the research is finished, however, you may see this information as described in the {***add hospital/clinical study site name here***}'s Notice of Information practices.

7. This Authorization does not have an expiration (ending) date.

8. You will be given a copy of this Authorization after you have signed it.

Print Name of Patient:
Signature of Patient / Legally Authorized Representative:
Date:

Signature of Witness:
Date:

8. IRB INFORMATION

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

9. OTHER INSTITUTIONS

There are no other institutions which are part of this clinical study other than the investigative sites, the Sponsor's independent contractor performing the economic healthcare analysis and designated core labs.

10. ADDITIONAL RECORDS AND REPORTS

The investigator and sponsor are responsible for maintaining the following accurate, complete, and current records relating to the investigation:

RECORDS	MAINTAINED BY INVESTIGATOR	MAINTAINED BY SPONSOR
All correspondence with another investigator, an IRB, the sponsor, a monitor, or the FDA	X	X
Shipments, receipts, and disposition of the ACPs	Packing lists, device accountability logs	Records of shipment and disposition of devices, copies of signed packing lists
ACP administration and use	Device accountability logs and CRFs	Copies of site's device accountability log and CRFs
Records of each subject's case history and exposure to the ACP	CRFs and source documentation	
Informed consent or documentation the device was used without consent	X	Documentation if the device was used without consent
The clinical Protocol and amendments, if any, and documentation of deviations from protocol	X	X
Adverse events and complaints	Adverse event CRFs and product incident reports along with IRB notifications and acknowledgement, if applicable	Adverse event CRFs and product incident reports along with IRB notifications and acknowledgement, if applicable
Signed Investigator agreements, financial disclosures, and mutual non-disclosure agreements	X	X
Any other FDA required records	X	X

The investigator/institution should take measures to prevent accidental or premature destruction of these documents. Study correspondence will be defined as documents pertaining to global study issues affecting the rights, safety, welfare, or scientific soundness of the study.

10.1 DOCUMENTING STUDY CORRESPONDENCE

Document phone conversations and file in the Regulatory Binder. Written hard copy correspondence from AGA Medical should also be filed in the Regulatory Binder.

10.2 RECORD RETENTION

Records are subject to FDA inspection and must be retained by Investigators for a period of two years after the latter of the following dates:

- 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

REPORTS	INVESTIGATOR	SPONSOR
Unanticipated Adverse Device Effects	To IRB and AGA Medical	To the FDA, all IRBs, and all Investigators within ten (10) working days after receiving notice of the event
Withdrawal of IRB Approval	To AGA Medical within five (5) working days	All IRBs and all Investigators will be notified within five (5) working days
Withdrawal of FDA approval		All IRBs and all Investigators will be notified within five (5) working days
Progress reports	To IRB and AGA Medical annually	To FDA and IRBs annually
Deviations from the Investigation Plan	IRB notification and acknowledgement (If applicable)	FDA if deviation affects the scientific soundness of the Investigational Plan
Informed consent	Use of device without consent must be reported to AGA and IRB within five (5) days	To the FDA within five (5) days working days of receipt of a device implant without informed consent
Final Reports	Investigators submit a final report to AGA Medical and the IRB within three (3) months after termination or completion of a study or the Investigator's part in a study	A Final Report will be sent to the FDA, all IRBs and Investigators within six (6) months after completion or termination
Other reports that may be requested by AGA or the IRB	Other reports that may be requested by AGA or the IRB	Reports that may be requested by IRB or FDA
Current Investigator List		Current Investigator List to the FDA every six (6) months following study initiation
Recall and device disposition		FDA and all IRBs will be notified within 30 working days of the reasons for any request that an Investigator return, repair, or dispose of any devices
Other	Investigators provide accurate, complete and current information about any aspect of the investigation	AGA Medical provides accurate, complete and current information about any aspect of the investigation upon request of the IRB or

	upon request of the IRB or FDA	FDA

The investigator must notify AGA Medical LLC prior to deleting any records relating to the ACP clinical trial. Sites will be notified when records no longer need to be retained.

10.3 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 days after the transfer occurs.

10.4 REPORTS

Investigators and sponsors are responsible for preparing and submitting the following complete, accurate, and timely reports;

These reports are subject to FDA inspection and the retention requirements.

IRB Records

Each reviewing IRB must maintain the following records:

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

APPENDIX: A - TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) PROTOCOL

(ALL views to be provided in the following sequence):

I. TEE Scanning Protocol (abbreviations listed at end of protocol)

The following TEE protocol is recommended to ensure uniformity across clinical study sites. TEE studies are to be performed at baseline, during the procedure, at the 45 day and 6 month follow-up visits. The TEE study should image the Left Atrium (LA) and Left Atrial Appendage (LAA) in multiple planes (i.e., 0°- ~110°). The purpose of the TEE is to obtain information regarding: a) LA/LAA thrombus; b) LAA ostium measurements; c) length distal to the LAA ostium; d) Flow into the LAA and e) to assess for procedural complications, such as device migration, pericardial effusion, etc.

II. Adjustment of the ultrasound instrument:

a. Adjust transmission power (gain) to minimize/eliminate “blooming” of specular reflectors.
b. Adjust the time gain compensation in such way that the image exhibits uniform brightness.
c. Adjust the color Doppler gain below the point where random color noise appears.
d. Set pulse repetition frequency with Nyquist velocity for CFD at ~35-45 cm/sec.
e. Use a velocity variance map with a “medium” color filter; set color tissue priority at a level that avoids overlay of color signals onto tissue structures.
f. Perform TEE at 5-7.5 MHz, with all other settings as mentioned above.
g. Perform both longitudinal and transverse plane sweeps to ensure full coverage of LA/LAA.
h. Record 3-5 consecutive beats for all cine-loop images; record at least 3-5 consecutive beats for all Doppler velocity tracings – record these as still frames (provide 2-3 still frames) at 100mm/s sweep speed.
i. Ensure that the ECG is recorded for all cine-loops and still-frame images.

III. TEE imaging study to be obtained in the following views:

a. The 5-chamber view (Omniplane 0°) with the aortic valve in the center of the screen and the LA in the right upper corner.
   - Standard 2D imaging
   - Zoom mode of LA and LAA; place color flow Doppler (CFD) around device to document communication between LA and LAA. (Post procedure only)
   - Zoom mode of LA and LAA; align Pulse Wave (PW) Doppler sample volume to record LAA-LA blood flow. The PW sample should be placed 0.5 to 1 cm from the ostium into the LAA.
   - 2D imaging of LV at mid-papillary muscle level (short axis), from gastric view.

b. The high LA/LAA view (Omniplane ~60°)

   Optional views (these may be difficult to obtain in some subjects):

   - Zoom mode of LA and LAA; place CFD around device to document communication

between LA and LAA. (Post procedure only)

- LA/LAA views; align PW Doppler sample volume to record LAA-LA blood flow. The PW sample should be placed 0.5 to 1 cm from the ostium into the LAA.

c. The longitudinal imaging plane (Omniplane ~80-110°) with LA/LAA in field of view.

- Zoom mode of LA and LAA; place CFD around device to document communication between LA and LAA. (Post procedure only)
- Zoom image of LA-LAA; align PW Doppler sample volume to record LAA blood flow. The PW sample should be placed 0.5 to 1 cm from the ostium into the LAA.

IV. Technical Notes for Completion of Echocardiographic Studies

a. Study subjects are to be identified only by study site and study subject number. This information will be entered in the ultrasound system patient data section in adherence to applicable privacy laws. No subject names should be displayed in the submitted studies.

b. Two-dimensional imaging to be performed in harmonic mode; the ECG tracing should be displayed on all images (still frames and cine-loops), clearly showing P wave/QRS morphology during the echocardiographic study. Avoid recording extrasystolic (PVC) beats.

c. For all spectral Doppler velocities, please use a display speed of 100 mm/sec, and optimize the velocity profile by moving the baseline up or down and showing the maximal velocity obtained at the top of the scale.

d. Clinical sites should retain a digital copy of the echocardiographic study in DICOM and the study should be analyzed locally. The Echocardiography Core Laboratory WILL NOT return submitted studies. An echocardiographic analysis WILL NOT be provided by the Echocardiography Core Laboratory to the clinical sites. The Echocardiography Core Laboratory Report will only be used for the purposes of the ACP study and NOT for diagnosis and/or clinical management of subjects enrolled in the ACP study.

V. Variables to be recorded by the study sites

a. Thrombus in the LA and/or LAA
b. LAA ostium measurements
c. Length distal to the LAA ostium
d. Spontaneous Echo Contrast (SEC) in the LA
e. Thrombus in the RA and/or RAA
f. Spontaneous Echo Contrast (SEC) in the RA
g. LAA-LA communication/flow (see E below)
h. Left Ventricular Ejection Fraction (LVEF)
i. Presence, location, and size of any aortic plaques
j. Mitral or aortic valve stenosis or regurgitation

k. In addition the following data points must also be documented: presence of
    1. Atrial septal defect
    2. Patent foramen ovale
    3. Prosthetic valve
    4. Intracardiac thrombus
    5. Atrial septal device

VI. Measurements to be analyzed by the Echocardiography Core Lab

a. Thrombus in the LA and/or LAA
b. LAA ostium measurements
c. Length distal to the LAA ostium
d. Thrombus in the RA and/or RAA
e. Spontaneous Echo Contrast (SEC) in the LA
f. Presence, location and size of any aortic plaque
g. LAA-LA communication/flow (see VII below)

VII. Assessment of Flow in Left Atrial Appendage

a. **None -** No color flow jet in or out of the LAA
b. **Small leak -** ≤ 3 mm diameter jet by color flow Doppler or multiple leaks which are cumulatively ≤ 3 mm diameter jet by color flow Doppler
c. **Large leak -** > 3 mm diameter jet by color flow Doppler or multiple leaks which are cumulatively > 3 mm diameter jet by color flow Doppler

APPENDIX: B - TRANSTHORACIC ECHOCARDIOGRAM (TTE) PROTOCOL

With the subjects in the left lateral position, standard transthoracic imaging should be obtained in the parasternal long-axis, parasternal short-axis, apical 4-chamber, apical 2-chamber and apical 3-chamber views. For the evaluation of left ventricular systolic function a sweep of the entire chamber from base to apex should be imaged from the parasternal short axis view. Evaluation of all 4 valves should include color flow Doppler, continuous and pulse wave Doppler interrogation. With the subjects lying supine, the atrial septum should be evaluated in the subcostal long axis view by both 2D imaging alone and with color flow Doppler.

Any post procedure complication such as pericardial effusion must be documented.

APPENDIX: C - AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR PROPHYLAXIS

PREVENTION OF INFECTIVE (BACTERIAL) ENDOCARDITIS
Wallet Card

This wallet card is to be given to patients (or parents) by their physician. Healthcare professionals: Please see back of card for reference to the complete statement.

Name: _____
needs protection from
INFECTIVE (BACTERIAL) ENDOCARDITIS
because of an existing heart condition.

Diagnosis: _____
Prescribed by: _____
Date: _____

You received this wallet card because you are at increased risk for developing adverse outcomes from infective endocarditis (IE), also known as bacterial endocarditis (BE). The guidelines for prevention of IE shown in this card are substantially different from previously published guidelines. This card replaces the previous card that was based on guidelines published in 1997.

The American Heart Association's Endocarditis Committee together with national and international experts on IE extensively reviewed published studies in order to determine whether dental, gastrointestinal (GI), or genitourinary (GU) tract procedures are possible causes of IE. These experts determined that there is no conclusive evidence that links dental, GI, or GU tract procedures with the development of IE.

The current practice of giving patients antibiotics prior to a dental procedure is no longer recommended **EXCEPT** for patients with the highest risk of adverse outcomes resulting from IE (see below on this card). The Committee cannot exclude the possibility that an exceedingly small number of cases, if any, of IE may be prevented by antibiotic prophylaxis prior to a dental procedure. If such benefit from prophylaxis exists, it should be reserved **ONLY** for those patients listed below. The Committee recognizes the importance of good oral and dental health and regular visits to the dentist for patients at risk of IE.

The Committee no longer recommends administering antibiotics solely to prevent IE in patients who undergo a GI or GU tract procedure.

Changes in these guidelines do not change the fact that your cardiac condition puts you at increased risk for developing endocarditis. If you develop signs or symptoms of endocarditis—such as unexplained fever—see your doctor right away. If blood cultures are necessary (to determine if endocarditis is present), it is important for your doctor to obtain these cultures and other relevant tests **BEFORE** antibiotics are started.

Antibiotic prophylaxis with dental procedures is reasonable only for patients with cardiac conditions associated with the highest risk of adverse outcomes from endocarditis, including:

- Prosthetic cardiac valve or prosthetic material used in valve repair
- Previous endocarditis
- Congenital heart disease only in the following categories:
  - –Unrepaired cyanotic congenital heart disease, including those with palliative shunts and conduits
  - –Completely repaired congenital heart disease with prosthetic material or device, whether placed by surgery or catheter intervention, during the first six months after the procedure*
  - –Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients with cardiac valvular disease

*Prophylaxis is reasonable because endothelialization of prosthetic material occurs within six months after the procedure.

Dental procedures for which prophylaxis is reasonable in patients with cardiac conditions listed above.

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa*

***Antibiotic prophylaxis is NOT recommended for the following dental procedures or events:** routine anesthetic injections through noninfected tissue; taking dental radiographs; placement of removable prosthodontic or orthodontic appliances; adjustment of orthodontic appliances; placement of orthodontic brackets; and shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa.

Antibiotic Prophylactic Regimens for Dental Procedures

Situation	Agent	Regimen—Single Dose 30-60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin **OR**	2 g IM or IV*	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—Oral regimen	Cephalexin**†	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

*IM—intramuscular; IV—intravenous
**Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin.

Gastrointestinal/Genitourinary Procedures: Antibiotic prophylaxis solely to prevent IE is no longer recommended for patients who undergo a GI or GU tract procedure, including patients with the highest risk of adverse outcomes due to IE.

Other Procedures: Procedures involving the respiratory tract or infected skin, tissues just under the skin, or musculoskeletal tissue for which prophylaxis is reasonable are discussed in the updated document (reference below).

Adapted from *Prevention of Infective Endocarditis: Guidelines From the American Heart Association,* by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. *Circulation,* 2007; 116: 1736-1754. Accessible at http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095.

Healthcare Professionals—Please refer to these recommendations for more complete information as to which patients and which procedures need prophylaxis.

ADA ACCEPTED American Dental Association

The Council on Scientific Affairs of the American Dental Association has approved this statement as it relates to dentistry.

American Heart Association. | American Stroke Association.
Learn and Live.

National Center
7272 Greenville Avenue
Dallas, Texas 75231-4596
americanheart.org

50-1605 0805

APPENDIX: D- CLINICAL INVESTIGATIONAL PLAN CHANGES DUE TO ENROLLMENT DISCONTINUATION

AGA Medical/St. Jude Medical has made the decision to discontinue further enrollments in the AMPLATZER Cardiac Plug (ACP) IDE trial. This decision was not a consequence of a safety or efficacy issue with the device or the study. All device subjects should continue to be followed per the protocol with the modifications noted below.

The following sections of the protocol are being changed due to the discontinuation of enrollment in the trial.

1.5 DURATION OF THE INVESTIGATION AND SAMPLE SIZE

A total of 97 subjects were enrolled in the trial at 17 centers. Safety data collected will be summarized in a final report. No additional subjects or centers will be added to the study.

2.12 FOLLOW-UP REQUIREMENTS

#3 From: For subjects randomized to control arm and those subjects who are randomized to device arm but do not undergo an implant attempt, follow-up windows are calculated based on the day of randomization. For subjects who undergo an implant attempt and/or receive the device, follow-up windows are calculated from the date of procedure. Subjects who are on warfarin should maintain an INR between 2-3 INR levels must be documented on an INR log.

To: Control subjects should be discontinued (exited) from the trial.

To: Device subjects who underwent an implant attempt, however did not receive the ACP device, should be discontinued (exited) from the trial.

To: Device subjects will have office visits through 2-years post-implant, and then telephone visits annually through 5 years post-implant. Once the subject has completed the 5 year telephone follow-up visit they should be discontinued (exited) from the trial.

#10 From: As part of the health economic and quality of life sub-study, hospital bills of enrolled subjects will be collected up to 2 years or until the study is completed.

To: The health economic and quality of life sub-study is being stopped. The collection of hospital bills is discontinued. The hospital bills collected for the index procedure will be analyzed.

2.12.1 ASSESSMENT AND FOLLOW-UP SCHEDULE; SUBJECTS WHO RECEIVE THE DEVICE

From:

	Procedure	Pre-discharge (+ 1 day)	45 days (+/-5 days)	3 Month (+/- 10 days) Post OAC Discontinuation Phone Visit [8]	6 months (+/- 30 days)	12 months (+/-30 days)	18 months (+/-60 days)	2 years (+/- 60 days)	Annually thereafter (+/- 60 days) phone visit [4]
Physical Exam		X	X		X	X	X	X	
Neurological Symptoms Interview			X		X	X	X	X	X [5]
Urine Pregnancy Test	X[1]								
12 lead Electrocardiogram		X	X		X	X	X	X	
2-D Color Flow Doppler Transthoracic Echo (TTE)		X				X [6]		X [6]	
Transesophageal Echocardiogram (TEE)	X		X		X	X [6]		X [6]	
MRI of head/brain [7]						X		X	
Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Medication Assessment [2]	X	X	X	X	X	X	X	X	X
INR Assessment [3]									
Quality of Life Assessment(s)						X		X	

To:

The following changes have been made to the assessment and follow-up table:

- The quality of life assessments have been removed.
- Added a note that monthly INR logs are only required for subjects that remain on warfarin.

	Procedure	Pre-discharge (+ 1 day)	45 days (+/-5 days)	3 Month (+/- 10 days) Post OAC Discontinuation Phone Visit [8]	6 months (+/- 30 days)	12 months (+/-30 days)	18 months (+/-60 days)	2 years (+/- 60 days)	Annually thereafter (+/- 60 days) phone visit [4]
Physical Exam		X	X		X	X	X	X	
Neurological Symptoms Interview			X		X	X	X	X	X [5]
Urine Pregnancy Test	X[1]								
12 lead Electrocardiogram		X	X		X	X	X	X	
2-D Color Flow Doppler Transthoracic Echo (TTE)		X				X		X [6]	
Transesophageal Echocardiogram (TEE)	X		X		X[6]	X [6]		X [6]	
MRI of head/brain [7]						X		X	
Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Medication Assessment [2]	X	X	X	X	X	X	X	X	X
INR Assessment [3]									

[1]Urine pregnancy test must be done within 24 hours prior to the procedure (for female subjects of childbearing potential)

[2]Review and record all and any changes to antiarrhythmic and antiplatelet medications

[3]INR must be tested within 24 hours prior to the procedure (for those subjects on warfarin). Post procedure- INR testing should commence 2-3 days after the initiation of warfarin therapy and be tested frequently until a stable dose / INR has been achieved and then at least every 4 weeks subsequently. Subjects are recommended to maintain a target INR between 2-3 while they are on warfarin (Monthly INR logs are not required once the subject stops taking warfarin)

[5]If during a telephone visit, an SAE is reported or a response of **Yes or Don't know** to any question on the Neurological Symptoms Interview is elicited an in-person interim office visit is required

[6]Refer to flowchart above

[7]MRI must include FLAIR, DWI, ADC maps, and GRE among other sequences. If subject is medically contraindicated to MRI, a CT of the head must be performed. If asymptomatic cerebral hemorrhage is detected through imaging, please note that there are no standardized clinical guidelines or treatment recommendation for the use of antithrombotic therapy based on MR Imaging findings. Subjects should be managed per institutional or investigator standard of care.

[8] This phone visit must be performed 3 months after a subject stops taking OAC (Note: OAC must be discontinued once no flow or ≤3mm jet into the LAA (via TEE) has been demonstrated

One week equals 7 days. One month = 30 days. One year= 365 days

2.15.3 Study Design

The study as designed was intended to determine the difference in efficacy and safety between the device and control arm (subjects treated with OMT).

There were three primary endpoints and hypotheses intended to be evaluated in the ACP clinical trial; these will no longer be analyzed as specified in the original trial protocol, rather, will be summarized as below:

1. From: An efficacy endpoint which compares the 2-year event rates of ischemic stroke and peripheral thromboembolism. This is a non-inferiority analysis where the device will be deemed efficacious if the risk ratio is < 1.75 or the risk difference in two years event rates is < 2.87.

To: This objective will not be analyzed as specified above. A summary of ischemic strokes and peripheral thromboembolism reported through 2 years of follow-up will be provided using descriptive statistics.

2. From: A long-term safety endpoint which compares long-term composite rates of all-cause mortality and major bleed. This is a superiority analysis where the

device will be deemed safe if the safety event rate in the device arm is proven superior to the safety event rate in the control arm (OMT).

To: This objective will not be analyzed as specified above. A summary of all-cause mortality and major bleeds reported through 2 years of follow-up will be provided using descriptive statistics.

3. From: An acute safety (short-term) endpoint which compares the rate of device or procedure related serious adverse events against a performance goal (PG). If this rate is less than 5%, the device is considered to have met the acute safety endpoint.

To: This objective will not be analyzed as specified. A summary of the device or procedure related serious adverse events reported through hospital discharge will be provided using descriptive statistics.

2.15.4 Analysis of Secondary Endpoints

From: Three comparisons for secondary endpoints will be made between OMT control group and the device group at the end of the trial. Secondary endpoints include: rate of transient ischemic attacks, asymptomatic intracerebral or intraventricular hemorrhage, atrial fibrillation status, device or procedure related adverse events, in-hospital procedure success, Day 45 clinical success, long-term clinical success, technical success and complete closure.

To: The following secondary endpoints will not be analyzed: rate of transient ischemic attacks, asymptomatic intracerebral or intraventricular hemorrhage, atrial fibrillation status, device or procedure related adverse events, in-hospital procedure success, Day 45 clinical success, long-term clinical success, technical success and complete closure.

2.15.6 Endpoints and Labeling

From: The following primary and secondary endpoints will be included in product labeling for the ACP device.

- Primary Effectiveness Endpoint
- Primary Safety Endpoint
- Secondary Endpoints

To: The endpoints will no longer be analyzed and hence no labeling claims are intended to be made.

2.15.7 Primary Analysis

From: Intent-to-treat analysis- Subjects are considered enrolled in the ACP clinical trial after informed consent and HIPAA authorization form or any other applicable permission form required by law has been signed and the subject has been randomized. All primary endpoint analyses will be based on the "intent-to-treat" principle. Specifically, subjects will be considered part of the intent-to-treat analysis population as long as they are randomized into the study, with no adjustment made for whether the device was implanted, compliance with treatment, or events occurring after randomization.

To: All device subjects will be summarized in a final report. Descriptive statistics will be used to summarize the analysis of all primary endpoints.

2.15.8 Secondary Analysis

From: In addition to the intent-to-treat analysis, secondary analyses will be performed on the three following analysis populations (two per protocol analyses and one as-treated).

To: The per-protocol analysis and the as treated analysis will not be performed.

2.15.9 Other Analyses

From: The following other analyses were planned: Subgroup analysis, Adverse Events Categorization, Residual Flow in LAA, Primary Effectiveness Component Analysis, Poolability Analysis, Center Effect, Analysis of Demographics, $CHADS_2$ Score Distribution, Time within therapeutic range (TTR) for INR subjects assigned to warfarin, Effect of Learning Curve, Handling of Missing Data, and Worst-case analysis.

To: The other analyses will not be performed due to the limited sample size and because control subjects will be discontinued (exited) from the trial.

2.16.2 DATA SAFETY MONITORING BOARD AND CLINICAL EVENTS COMMITTEE

From: Both an independent Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC) will be utilized to regularly review study progress with regard to safety. The CEC will be blinded to subject's treatment assignment. Members of these boards cannot be investigators on the ACP Clinical Trial. Board membership includes: cardiologists, neurologists, and biostatisticians. The primary responsibilities of the DSMB and CEC include:

- Review and refine adverse event definitions as necessary during the conduct of the clinical investigation

- Review and adjudicate adverse events and primary endpoints as they occur over the course of the clinical investigation
- Review and validate the subject sample (i.e., review inclusion/exclusion deviations and other protocol deviations)
- Provide oversight for issues affecting general subject welfare
- Recommend premature study termination

To: The Data Safety Monitoring Board (DSMB) will continue to review and adjudicate all adverse events and oversee safety of the trial. As blinding is no longer necessary to prevent bias, the Clinical Events Committee will no longer review events, and their responsibilities will be absorbed by the DSMB.

2.16.5 BLOOD WORK CORE LAB

From: An independent core lab will be utilized to perform baseline hematology and coagulation tests (as described in section 2.9). Members of the Blood Work Core Lab will have no affiliation with the ACP Clinical Trial.

To: This independent core lab will be closed as all of the baseline coagulation samples have been analyzed.

2.29 ECONOMIC AND QUALITY OF LIFE SUB-STUDY

From: In conjunction with the pivotal phase of clinical study, the costs and benefits of treatment will be evaluated through an economic and quality of life analysis. Medical resource use, cost and health-related quality of life within the trial period will be compared between treatment groups. If ACP therapy is found to be effective, its long term cost-effectiveness analysis will be assessed. The economic and quality of life analysis will be fully integrated into the clinical trial, with a common informed consent form and collection of subject reported resource use in the case report form. Hospital bills reporting hospital care for study subjects during the study period will also be collected at least through 2 years and until the study is completed.

To: The health economic sub-study will be stopped. Hospital bills were collected for all index procedures. No additional hospital bills or quality of life questionnaires will be collected.