Abbott	Clinical Investigation Plan Cover Page

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AMPLATZER™ Cardiac Plug Observational Post-Approval Study
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Sponsor

Abbott Medical
5050 Nathan Lane North
Plymouth, MN 55442
USA

[redacted]

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ACP PAS China

AMPLATZER™ Cardiac Plug Observational Post-Approval Study

Clinical Investigation Plan (CIP)

Sponsor

St. Jude Medical Coordination Center BVBA
The Corporate Village Da Vincilaan 11 - Box F1
1935 Zaventem,
Belgium

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1.0 SYNOPSIS

Title:	AMPLATZER™ Cardiac Plug Observational Post-Approval Study
Acronym:	ACP PAS China
Purpose:	To observe the safety and effectiveness of the AMPLATZER™ Cardiac Plug (ACP) device in Chinese population indicated for use of AMPLATZER™ Cardiac Plug after its market approval by China FDA (CFDA).
Objectives:	Primary Objectives (1) To evaluate short term (0 - 7 days post-procedure) safety of AMPLATZER™ Cardiac Plug implantation in Chinese population (2) To evaluate long term safety of AMPLATZER™ Cardiac Plug implantation in Chinese population through 2 years (3) To evaluate effectiveness of AMPLATZER™ Cardiac Plug implantation in Chinese population through 2 years
	Additional Objectives (1) To evaluate the occurrence of ischemic stroke or systemic embolism through 5 years in Chinese population implanted with AMPLATZER™ Cardiac Plug (2) To evaluate long term safety of AMPLATZERTM Cardiac Plug implantation in Chinese population through 5 years (3) To evaluate immediate successful implantation rate of the AMPLATZER™ Cardiac Plug in the left atrial appendage (LAA) during the procedure
Endpoints:	***Primary Endpoints*** 1. Short Term Safety Major adverse events within 7 days after the procedure: short term occurrence of death, stroke (ischemic or haemorrhagic), systemic embolism, or procedure or device-related complications requiring major cardiovascular or endovascular intervention. 2. Long Term Safety The 2-year occurrence of device embolization, device erosion, clinically significant device interference with surrounding structure, device thrombus, device fracture, device infection (endocarditis / pericarditis), device perforation, device laceration, or device allergy. 3. Effectiveness The 2-year rate of the composite of ischemic stroke or systemic embolism
	Descriptive Endpoints 1. Rate of ischemic stroke or systemic embolism through 5 years post-implant 2. Occurrence of composite of damage to blood vessel or organ or damage to adjacent organs at implant, device dislodgement, device

	fracture, device erosion, or pericardial tamponade through 5 years post-procedure 3. Device success rate - defined as device deployed and implanted in correct position 4. Rate of closure of the left atrial appendage - defined as residual jet around the device of ⩽ 5mm, based on the 45-day TEE
Design:	This is a prospective, multi-centre, single arm, post approval, observational study. The clinical study will be conducted at up to 35 sites in China. Approximately 343 subjects will be enrolled in this study. (1) Patients who are eligible for an ACP based on the approved indications can be enrolled in this study. (2) Each patient will be followed up for 5 years. (3) Baseline, procedure, and pre-discharge evaluations will be required. (4) Hospital visit will be required at 45 days, 6 months, 12 months and 24 months. (5) The 36-, 48- and 60-month follow up visits will be conducted by telephone contact with proper record. The total study duration is expected to be approximately 7 years; this observational study will begin enrolment in Q4 of 2016. Per CFDA requirement, an annual report of ADE and SADE observed in this study will be submitted to CFDA. **Testing required:** ▪ **Baseline evaluation**: Informed consent, cardiovascular and medical history, physical examination, 12-lead electrocardiogram (ECG),CHA2DS2-VASc score and individual components of the score, HAS-BLED score, Neuroimaging (brain MRI or CT scan), modified Rankin Scale and medication assessment ▪ **Procedure**: Transesophageal echocardiogram (TEE), Angiogram, medication and adverse event (AE) assessment ▪ **Post procedure/Pre-Discharge:** Transthoracic echocardiogram (TTE), medication assessment, AE assessment ▪ **45day** (+45 days): TEE, medication assessment, AE assessment ▪ **6M** (+/- 3 weeks): Medication and AE assessment ▪ **12M** and **24M** (+/- 6 weeks): Medication and AE assessment ▪ **36M, 48M and 60M**(+/- 6 weeks): Phone contact follow-up for medication and AE assessment ▪ **Interim/unscheduled visits:** Per subject or physician discretion **Suspected Stroke / TIA Evaluation:**

	▪ All subjects suspected of a stroke should be seen by a stroke neurologist for evaluation and appropriate neurological testing (i.e. magnetic resonance imaging (MRI), computed tomography (CT)) ▪ In the event of a confirmed stroke or TIA, the modified Rankin Scale assessment should be performed 90 days after the event and a TEE should be conducted to verify the presence of device-related thrombus within 14 days from the date the site becomes aware of the event
Justification for study design	A single-arm observational study is appropriate to observe the safety and effectiveness of the ACP device in the post-market setting in China. The study includes a short-term safety endpoint, a long-term safety endpoint, and a long-term effectiveness endpoint. The safety and effectiveness endpoints in this study are consistent with those reported for other studies or publications on left atrial appendage occlusion. The short-term safety endpoint was chosen to reflect serious procedure-related complications during the implant procedure for the ACP device, resulting in either surgical or endovascular intervention. This endpoint appropriately captures important procedural complications and adequately characterizes the short-term safety profile of the procedure and the device. The long-term safety endpoint is set at 24 months to capture long-term complications associated with the ACP device. This safety endpoint is based on the recently released Eurointervention consensus document[34] on definitions, endpoints and data collection requirements for left atrial appendage occlusion clinical studies Finally, the effectiveness endpoint appropriately reflects the occurrence of types of events (ischemic stroke or systemic embolism) that the device is intended to prevent. This endpoint is consistent with other studies and publications on left atrial appendage occlusion. The performance goals for this study have been established primarily based on publications on the ACP device. [redacted] Additional descriptive endpoints have been specified to characterize the mechanism of action of the device (i.e., device closure) and the long-term effects of device implant through 5 years.
Devices used:	The AMPLATZER™ Cardiac Plug is a transcatheter, self-expanding device intended for use in preventing thrombus embolization from the left atrial appendage. The device is constructed from a nitinol mesh and consists of a lobe and a disc connected by a central waist. The device is

	designed to facilitate occlusion. 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 cables. The device has radiopaque markers at each end and at the stabilizing wires. **Device Sizes:** 16, 18, 20, 22, 24, 26, 28, and 30 mm (lobe diameter) **Delivery System**: AMPLATZER TorqVue® 45º x 45º (sheath sizes 9, 10, or 13 Fr)
Study Population	Patients who have non-valvular atrial fibrillation (NVAF) and are contraindicated to long-term oral anticoagulant; or patients who experience stroke or relevant event despite taking warfarin.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> • Patient who meets the current indications and per physician discretion for ACP implant • Patient who is ≥ 18 years of age at the time of enrolment. • Patient who is able to provide written Informed Consent prior to any study related procedures. <u>Exclusion Criteria</u> • Patient who is unable to comply with the follow-up schedule • Patient with the presence of intracardiac thrombus • Patient with active endocarditis or other infections producing bacteraemia • Patient who has low risk of stroke (CHA2DS2-VASC score is 0 or 1) or low risk of bleeding (HAS-BLED score<3) • Patient where placement of the device would interfere with any intracardiac or intravascular structures • Patient who is under medical conditions not appropriate to participate in the study in the opinion of the investigator • Subject with LAA anatomy that does not accommodate a device per the sizing guidelines • Patient who has a life expectancy of less than 2 years due to any condition • Patient who are currently participating in a clinical investigation that includes an active treatment arm.

	• Patient who already had a left atrial appendage closure device implanted prior to the study
Sample Size Estimation	**Primary Safety Endpoint(Short Term)** The following hypothesis will be tested: H_0: $p_s \geq PG_s$ H_1: $p_s < PG_s$ where p_s is the proportion of subjects undergoing the ACP LAA closure procedure, who experience an acute safety endpoint event. p_s will be estimated as a binomial proportion. The assumption for the primary safety endpoint event rate is based on outcomes in [redacted] The performance goal, PG_s, in this hypothesis is set at 10%. [redacted] The sample size required to reject the null hypothesis [redacted] is 231 subjects. [redacted] **Primary Safety Endpoint (Long-Term)** The following hypothesis will be tested: H_0: $p_l \geq PG_l$ H_1: $p_l < PG_l$ where p_l is the long-term safety endpoint event rate. [redacted]

[redacted] The performance goal, PG_I, is set at 10%, [redacted] 308 subjects are required to be enrolled in the study.

[redacted]

Primary Effectiveness Endpoint:

The following hypotheses will be tested:

H_0: $p_e \geq PG_e$

H_1: $p_e < PG_e$

where p_e is the event rate at 24 months. [redacted] The performance goal, PG_e is set at 9%, [redacted] 343 subjects are required to be enrolled in the study.

[redacted]

[redacted]

[redacted]

2.0 INTRODUCTION

This document is a clinical investigational plan for St. Jude Medical's AMPLATZER™ Cardiac Plug (ACP) device post-approval observational study in the Chinese population. China FDA (CFDA) approved the ACP device in Sep 2015 and required a post-approval study of the ACP device to observe the safety and effectiveness of the ACP device in Chinese population indicated for use of ACP device after its market approval. The sponsor of this study is St. Jude Medical Coordination Center BVBA.

3.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder[1]. During AF there are multiple simultaneous waves of contractions, which spread in a chaotic manner through both atria. This arrhythmia results in rapid, uncoordinated contractions, which decrease the blood pumped through the atria. The loss of mechanical efficiency during AF leads to insufficient contractions in the left atrium (LA)[2]. Stagnation of blood flow in the LA leads to hypercoagulability and thus increases the risk for thrombus formation in the LA or left atrial appendage (LAA). Approximately 90% of all the thrombi in subjects with non-valvular AF (NVAF) forming in the LA originate in the left atrial appendage[3]. The thrombus formation, in turn exposes the patient to thromboembolic events.

Echocardiographic risk factors for LAA thrombus formation include echocardiographic evidence of decreased LAA flow velocity and spontaneous echo contrast within the left atrium and left atrial appendage[4,5]. 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[2]. Agmon et al. found that the relative risk reduction of ischemic stroke was 2.6 times greater in patients with LAA flow velocities <20cm/s[2] than those with higher LAA velocites[6].

Non-valvular AF patients have been assessed to determine the risk of stroke based on the presence of independent risk factors. In a study by Gage et al. the $CHADS_2$ index was shown to be a tool to predict the risk of stroke in subjects with AF[7]. 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 transient ischemic attack (TIA). The study found that AF patients who were not treated with anti-thrombotic agents had an increased risk of stroke ranging from 1.9% to 18.2% as $CHADS_2$ scores increase from 0 to 6.

A study by Go et al. reviewed outcome data (11,526 patients) in a large primary care setting and confirmed that thromboembolic risk increases progressively with $CHADS_2$ score[8]. The study also noted that oral anticoagulation with warfarin reduces the risk of stroke in most patients with the exception of those at lowest risk ($CHADS_2$ score of zero) and highest risk ($CHADS_2$ >5) for stroke. The more recently developed CHA_2DS_2-VASc risk assessment scheme[9], which identifies truly low risk subjects, assigns two points to age $\geq$75 years and previous stroke, TIA or thromboembolism and one point each to congestive heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease, age between 65-74 years and female sex. A recent validation[10] of these risk schemes in more than 90,000 patients without oral anticoagulation (OAC) but on aspirin showed annual ischemic stroke rates ranging from 0.6% in CHA_2DS_2-VASc = 1 to 4.8% in CHA_2DS_2-VASc = 4, and more than 12% for CHA_2DS_2-VASc = 9.

In a meta-analysis conducted by Andersen et al., warfarin was found to be superior to aspirin and placebo in reducing the risk of systemic embolism in subjects with NVAF[11]. Hart et al. reported that adjusted dose warfarin reduces stroke risk by 64% (6 trials) and antiplatelet agents reduce stroke risk by 22%[12]. The study also reported that risk of intracranial hemorrhage was doubled with adjusted-dose warfarin compared with aspirin.

Recently, new drugs (known as novel oral anticoagulant, or NOAC) have been developed with less dietary and pharmacological interactions than warfarin and less stringent requirements for frequent INR monitoring. Major trials such as RE-LY and ROCKET AF demonstrated that dabigatran and rivaroxaban are non-inferior to warfarin in the prevention of stroke or systemic embolism[13, 14]. The ARISTOTLE trial demonstrated apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in subjects with atrial fibrillation[15]. The ENGAGE AF-TIMI[16] trial demonstrated both once daily dose regimens of edoxaban were noninferior to warfarin with respect to the preventions of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes[17]. A number of characteristics that increase a patient's risk for stroke also increase the patient's risk for bleeding, therefore an alternative to warfarin and NOAC drugs is needed.

Left atrial appendage occlusion (LAAO) is considered a viable alternative to oral anticoagulation (OAC) therapy for stroke prevention in patients with NVAF[15-25]. Published evidence supporting LAAO is provided in large part by the major randomized controlled trials PROTECT AF and PREVAIL[15-18]. Five-year results of PROTECT AF showed superiority of the WATCHMAN™ device in mortality and stroke reduction compared to optimal medical treatment with warfarin[18].

AMPLATZER™ Cardiac Plug device

The ACP device (St Jude Medical, St. Paul, MN, USA) is a self-expandable nitinol device, with fixation anchors. The ACP device is a first generation device based on AMPLATZER occluder technology specifically designed for LAAO.

The AMPLATZER Cardiac Plug demonstrated favorable feasibility and safety in observational studies in Europe[26-28]. Additionally, Park et al. reported the results of an investigator-initiated retrospective study to report on the initial European experience in patients treated with the AMPLATZER Cardiac Plug device between December 2008 and November 2009. SJM's AMPLATZER Cardiac Plug Registry results were also presented at EURO PCR in 2012 and 2014[29-30]. In addition, results from a multicenter study involving 22 sites and 1047 consecutive patients undergoing implant of the AMPLATZER Cardiac Plug device showed a high procedural success rate and a favorable outcome for the prevention of AF related thromboembolism[31].

In a comparative study between the AMPLATZER Cardiac Plug and the WATCHMAN devices (40 patients each), Chun et al.[32] found the devices to perform similarly. The rate of successful implantation achieved with the ACP device was greater than with the WATCHMAN device (100% vs. 95%) although the difference was not statistically significant. TEE at follow-up revealed a significantly higher incidence of residual peri-device flow (jet > 5 mm) for the WATCHMAN device compared to the ACP device, although this was not associated with an increased incidence of thromboembolic events. This finding is consistent with other reports on the ACP device[33].

In conclusion, percutaneous LAAO devices have emerged as an alternate option for stroke risk reduction in non-valvular AF patients at high risk for stroke or not suitable for long-term oral anticoagulant.

Certificate History

Date	Action
29 September 2015	CFDA license
16 October 2012	CE Mark

4.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

4.1 DESCRIPTION OF SUBJECT POPULATION

The population intended for this study is patients who have NVAF and are contraindicated to long-term oral anticoagulant, or patients who experience stroke or relevant event despite taking warfarin.

4.2 ANTICIPATED CLINICAL BENEFITS

Patients suitable to receive the ACP device should be deemed by their physician to have an appropriate rationale to seek an alternative to pharmocologic therapy such as the inability to tolerate long term OAC. The ACP device is intended to be an alternative when long term OAC therapy is unacceptable. A potential benefit of receiving an LAAO device is avoiding long-term OAC, thereby lowering the risk of bleeding. The close follow-up by subjects' treating physicians is a potential benefit for the subject of participating in this clinical study.

4.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Anticipated adverse events and adverse device effects may occur during and after the ACP device implant procedure. Adverse event definitions are provided in Section 9 and Appendix G. Refer to IFU for a complete list of potential anticipated adverse events**.**

4.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

Risks associated with participating in this clinical study are expected to be no different from risks associated with undergoing ACP device implant which is a commercially available transcatheter device in China.

4.5 RESIDUAL RISKS ASSOCIATED WITH THE DEVICE

The ACP device is market approved in China where the study will be conducted. The risk profile of the ACP device implant procedure is described in the IFU.

4.6 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

The Sponsor will select investigators qualified by training and experienced to participate in this study. Participating sites will be selected based upon qualifications of the primary investigator. During the study, sites may be subject to quality assurance audits by the Sponsor (or designee), as well as monitoring visits to assess data integrity and study compliance. Additionally, the study will have an

appointed SJM Clinical Safety team that will review and adjudicate all reported serious adverse events. The SJM Clinical Safety team will advise regarding the safety of study subjects.

4.7 RISK-TO-BENEFIT RATIONALE

Risks associated with participating in this clinical study are no different from risks associated with undergoing LAAO implant with a commercially available transcatheter device. The close follow-up by subjects' treating physicians is a potential benefit for the subejct of participating in this clinical study.

5.0 STUDY DESIGN

5.1 PURPOSE

To observe the safety and effectiveness of the AMPLATZER ™ Cardiac Plug device in Chinese population indicated for use of AMPLATZER ™ Cardiac Plug after its market approval by China FDA (CFDA).

5.2 STUDY DESIGN AND SCOPE

This is a prospective, multi-centre, single arm, post-approval observational study.

5.2.1 Number of subjects required to be included in the study

Approximately 343 subjects will be enrolled at up to 35 sites in China in the study (refer to section 13.0 STATISTICAL CONSIDERATIONS).

5.2.2 Estimated time needed to enroll this subject population

The total study duration is expected to be approximately 7 years, dependent on the rate of enrollment and the regulatory timeline. This study will begin enrolment in Q4 of 2016.

5.2.3 Justification for study design

A single-arm observational study is appropriate to observe the safety and effectiveness of the ACP device in the post-market setting in China. The study includes a short-term safety endpoint, a long-term safety endpoint, and a long-term effectiveness endpoint.

The safety and effectiveness endpoints in this study are consistent with those reported for other studies or publications on left atrial appendage occlusion.

The short-term safety endpoint was chosen to reflect serious procedure-related complications during the implant procedure for the ACP device, resulting in either surgical or endovascular intervention. This endpoint appropriately captures important procedural complications and adequately characterizes the short-term safety profile of the procedure and the device.

The long-term safety endpoint is set at 24 months to capture long-term complications associated with the ACP device. This safety endpoint is based on the recently released EuroIntervention consensus document[34] on definitions, endpoints and data collection requirements for left atrial appendage occlusion clinical studies

Finally, the effectiveness endpoint appropriately reflects the occurrence of types of events (ischemic stroke or systemic embolism) that the device is intended to prevent. This endpoint is consistent with other studies and publications on left atrial appendage occlusion.

The performance goals for this study have been established primarily based on publications on the ACP device. Information has also been provided to support these performance goals based on outcomes with the WATCHMAN™ device.

Additional descriptive endpoints have been specified to characterize the mechanism of action of the device (i.e., device closure) and the long-term effects of device implant through 5 years.

5.3 OBJECTIVES

5.3.1 Primary Objectives

(1) To evaluate short term (0 - 7 days post-procedure) safety of AMPLATZER™ Cardiac Plug implantation in Chinese population.

(2) To evaluate long term safety of AMPLATZER™ Cardiac Plug implantation in Chinese population through 2 years.

(3) To evaluate effectiveness of AMPLATZER™ Cardiac Plug implantation in Chinese population through 2 years.

5.3.2 Additional Objectives

(1) To evaluate the occurrence of ischemic stroke or systemic embolism through 5 years in Chinese population implanted with AMPLATZER™ Cardiac Plug

(2) To evaluate long term safety of AMPLATZER™ Cardiac Plug implantation in Chinese population through 5 years

(3) To evaluate the immediate successful implantation rate of the AMPLATZER™ Cardiac Plug in the left atrial appendage (LAA)

5.4 ENDPOINTS

5.4.1 Primary Endpoints

1. Short Term Safety
   Major adverse events within 7 days after the procedure: short term occurrence of death, stroke (ischemic or haemorrhagic), systemic embolism or procedure or device-related complications requiring major cardiovascular or endovascular intervention.

2. Long Term Safety
   The 2-year occurrence of device embolization, device erosion, clinically significant device interference with surrounding structure, device thrombus, device fracture, device infection (endocarditis and pericarditis), device perforation, device laceration, or device allergy.

3. Effectiveness
   The 2-year rate of the composite of Ischemic stroke or systemic embolism

5.4.2 Descriptive Endpoints

1. Rate of ischemic stroke or systemic embolism through 5 years post-implant
2. Occurrence of composite of damage to blood vessel or organ or damage to adjacent organs at implant, device dislodgement, device fracture, device erosion, or pericardial tamponade through 5 years post-procedure
3. Device success rate- defined as device deployed and implanted in correct position
4. Rate of closure of the LAA - defined as residual jet around the device of ≤ 5mm, based on the 45-day TEE

5.5 INCLUSION AND EXCLUSION CRITERIA

A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.

All subjects enrolled in the study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification number linked to their names, alternative identification or contact information.

This log will be kept up to date throughout the clinical study by the principal investigator or his/her authorized designee. To ensure subject privacy and confidentiality of data this log must be maintained throughout the clinical study at the clinical site.

5.5.1 Inclusion Criteria

To participate in this clinical subject, the subject must meet all of the following inclusion criteria:

- Patient who meets the current indications and per physician discretion for ACP implant
- Patient who is ≥ 18 years of age at the time of enrolment
- Patient who is able to provide written Informed Consent prior to any study related procedures.

5.5.2 Exclusion Criteria

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria:

- Patient who is unable to comply with the follow-up schedule.
- Patient with the presence of intracardiac thrombus
- Patient with active endocarditis or other infections producing bacteraemia
- Patient who has low risk of stroke (CHA2DS2-VASC score is 0 or 1) or low risk of bleeding (HAS-BLED score<3)
- Patient where placement of the device would interfere with any intracardiac or intravascular structures
- Patient who is under medical conditions not appropriate to participate in the study in the opinion of the investigator.
- Patient with LAA anatomy that does not accommodate a device per the sizing guidelines
- Patient who has a life expectancy of less than 2 years due to any condition

- Patient who are currently participating in a clinical investigation that includes an active treatment arm
- Patient who already had a left atrial appendage closure device implanted prior to the study

5.6 INFORMED CONSENT PROCESS

Prior to enrolling in the clinical study and conducting device implant procedure, all subjects will be consented, as required by applicable regulations and the site's IRB/EC. Informed consent must be obtained from each subject prior to device implant procedure. The consent form must be signed and dated by the subject and by the person obtaining the consent.

The principal investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's IRB/EC. Failure to obtain informed consent from a subject prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the site's IRB/EC/ consistent with the site's IRB/EC reporting requirements.

6.0 DEVICE

6.1 DEVICE DESCRIPTION

AMPLATZER™ Cardiac Plug (**Figure 1**) is a transcatheter, self-expanding device intended for use in preventing thrombus embolization from the left atrial appendage. The device is constructed from a nitinol mesh and consists of a lobe and a disc connected by a central waist. The device is designed to facilitate occlusion. 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 cables. The device has radiopaque markers at each end and at the stabilizing wires.

The ACP device is recommended for use with the AMPLATZER TorqVue® 45º x 45º Delivery Sheath.

Refer to the Figure1 and Table 1 as below and IFU for more information about the device.

Figure 1: The ACP device and key components

A. Screw attachments
B. Waist of device
C. Lobe
D. Marker Bands
E. Stabilizing wires
F. Platinum thread
G. Disc

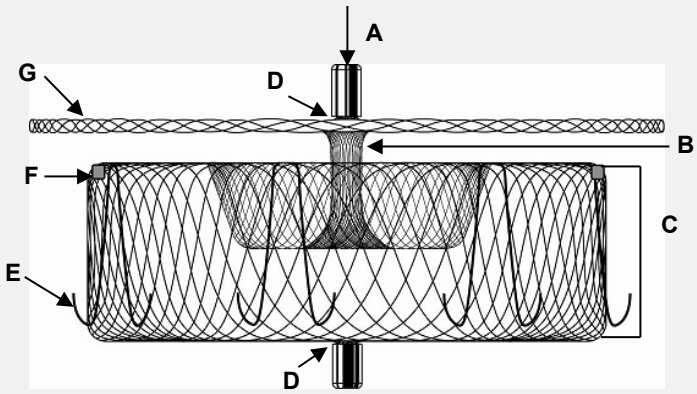

Table 1: Model numbers and key dimensions of the ACP device and delivery system

Part Number	ACP Lobe/ Device Size	Left Atrial Disc Size (mm)	Lobe Length (mm)	TorqVue Delivery System
9-ACP-007-016	16mm	20	6.5	9F
9-ACP-007-018	18mm	22	6.5	10F
9-ACP-007-020	20mm	24	6.5	10F
9-ACP-007-022	22mm	26	6.5	10F
9-ACP-007-024	24mm	30	6.5	13F
9-ACP-007-026	26mm	32	6.5	13F
9-ACP-007-028	28mm	34	6.5	13F
9-ACP-007-030	30mm	36	6.5	13F

6.2 DEVICE ACCOUNTABILITY (if applicable)

The ACP device has been approved by CFDA and is commercially released in China. Therefore, there are no additional tracking requirements for this study. Information regarding opened, introduced, and implanted devices will be recorded in the Procedure eCRF and out of service eCRF in case of explant.

6.3 DEVICE HANDLING AND STORAGE

Please refer to IFU.

7.0 PROCEDURES

This study will be conducted in accordance with the clinical protocol and IFU. All persons participating in the conduct of the study will be qualified by education, training, or experience to perform study-related tasks.

The study will not commence until SJM receives written approval from the EC and relevant regulatory authorities, and all required documents have been collected from the participating sites.

Figure 2 below describes the study flowchart for subject screening, consent, enrollment and follow-up through the 5-year follow-up visit. **Table 2** below outlines the testing and assessments required per study visit interval for subjects who are implanted with an ACP device. **Table 3** below outlines the eCRFs to be completed for subjects and as per the recommended study visit intervals.

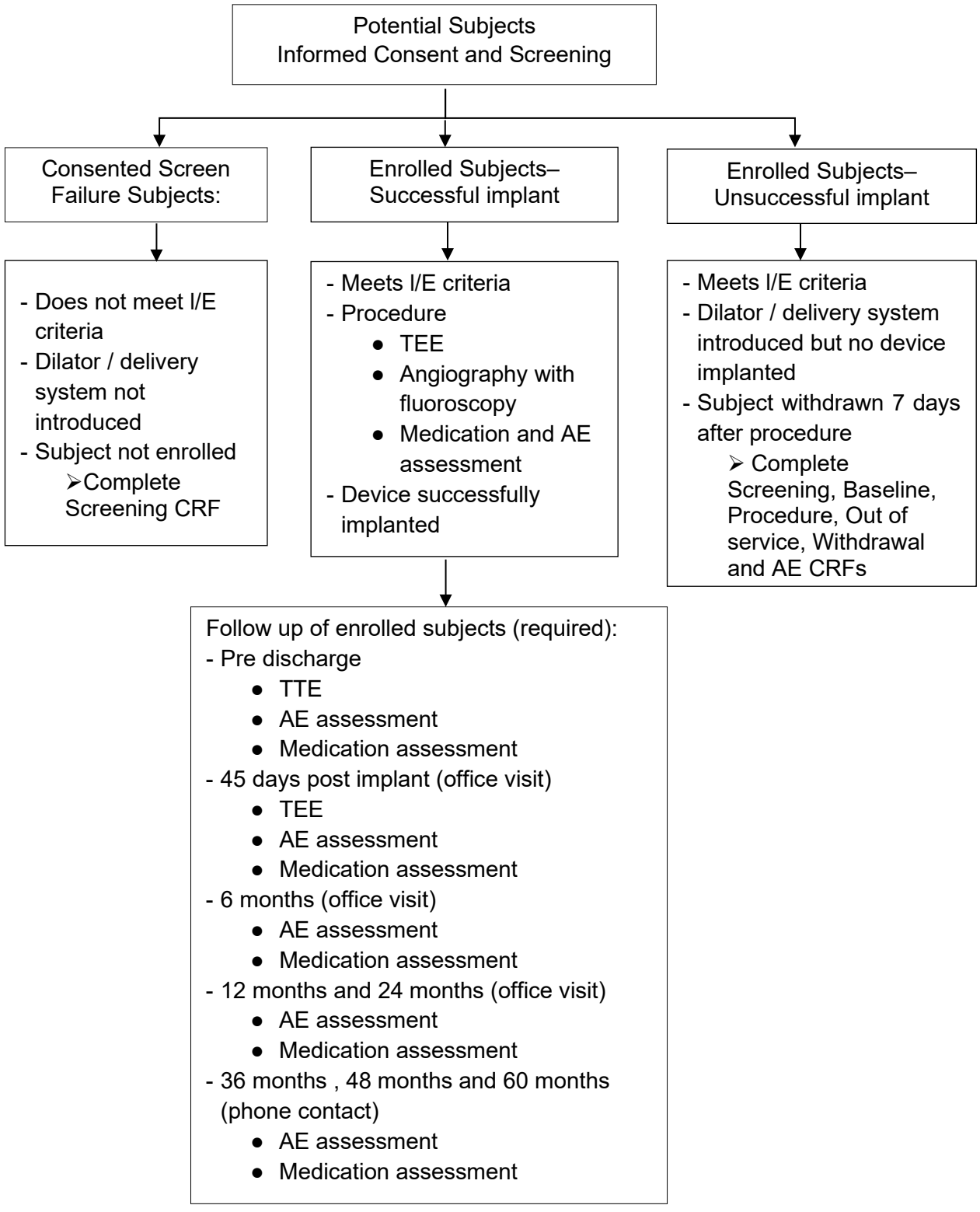

Figure 2: Study flowchart for subject screening, consent, enrollment and follow-up

Table 2: Study visits and activities

Visits / Study Activities	Screening &Enrollment & Baseline	Procedure	Post-Procedure/ Pre-Discharge	45 days (+ 45 days)	6M (+/- 3 weeks)	12M, 24M (+/- 6 weeks)	36M,48M and 60M (+/- 6 weeks, Phone contact)	Interim/ unscheduled Follow-up
Informed Consent Process	X							
- Physical examination - Cardiovascular and medical history - CHA_2DS_2-VASc score - HAS-BLED score	X							
12-lead ECG	X							
Medication[3] Assessment	X	X	X	X	X	X	X	X
Angiography		X						
TTE			X					
TEE	X[1]	X		X				X[2]
Neuroimaging (brain MRI or CT scan)	X[4]							
Modified Rankin Scale	X							X[5]
Adverse Event Assessment		X	X	X	X	X	X	X

[1]The Baseline TEE is optional if a TEE is performed on the day of procedure to rule out the presence of intracardiac thrombus (including left atrial appendage thrombus) and to assess the size and shape of the LAA. If an exclusion is noted on the TEE and the procedure does not occur, the patient is not enrolled.

[2]If stroke or TIA is confirmed, complete TEE within 14 days after the awareness of the event.

[3]Assessment for antithrombotic medication

[4] Neuroimaging can be performed any time from 2 months prior to implant

[5]Perform modified Rankin Scale assessment 90 days after a confirmed stroke or TIA

Table 3: Study visits and electronic case report forms

Visits / eCRF	Screening &Enrollment & Baseline	Procedure	Post-Procedure/ Pre-Discharge	45 days	6M	12M and 24M	36M, 48M and 60M	Interim/ unscheduled Follow-up
Baseline	**X**							
Screening	**X***							
Procedure		**X**						

Visits / eCRF	Screening &Enrollment & Baseline	Procedure	Post-Procedure/ Pre-Discharge	45 days	6M	12M and 24M	36M, 48M and 60M	Interim/ unscheduled Follow-up
Follow Up			**X**	**X**	**X**	**X**	**X**	**X****
Medication	**X**		**X**	**X**	**X**	**X**	**X**	**X****

**for screening failure subject, only screening eCRF is required to be completed.*
***Complete if stroke or TIA is confirmed*

Additional eCRFs, reports and assessment noted below should be completed upon occurrence, and/or as applicable:

- Withdrawal eCRF
- Adverse Event eCRF
- Protocol Deviation eCRF
- Death eCRF
- Out of service eCRF
- Modified Rankin Scale (Appendix H) (complete 90 days after confirmed stroke or TIA)

If a stroke/TIA is suspected, the subject should be seen by a stroke neurologist for evaluation and appropriate neurological testing (i.e. CT or MRI, and CTA or MRA). If a stroke or TIA is confirmed, the modified Rankin Scale eCRF should be completed 90 days after the event and a TEE is required within 14 days from the date the site becomes aware of the event to confirm device placement, LAA flow parameters and presence/absence of device-related thrombus.

7.1 SCREENING & ENROLLMENT & BASELINE VISIT

The following baseline and enrollment activities are performed as part of the screening process:

- Informed consent process
- Physical examination
- Cardiovascular and medical History
- CHA_2DS_2-VASc score

CHA_2DS_2-VASc	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior myocardial infarction, peripheral artery disease or aortic plaque]	1
Age 65-74	1
Sex category [i.e. female gender]	1

- HAS-BLED score:

HAS-BLED	Score
Hypertension history (uncontrolled, > 160 mmHg systolic)	1
Abnormal renal function/renal disease (dialysis transplant, creatinine > 2.6 mg/dL or > 200µmol/L)	1

Liver disease (cirrhosis, bilirubin > 2x normal AST/ALT/AP > 3x normal)	1
Stroke history	1
Bleeding, anemia, or predisposition to bleeding	1
Labile INR (Unstable/high INR's, or poor time (< 60% time in therapeutic range)	1
Elderly - Age ≥ 65 years	1
Drugs - Medication usage predisposing to bleeding (antiplatelet agents, NSAIDs)	1
Alcohol usage history (> 8 drinks/week)	1

- 12-lead ECG
- TEE (optional if a TEE is performed on the day of procedure)
- Antithrombotic medication assessment
- Neuroimaging (brain MRI or CT scan)
- Modified Rankin Scale

The principal investigators or delegated study personnel are responsible for screening all potential subjects to determine subject eligibility for the study. If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the study and cannot be enrolled. The subject is enrolled in the study when consent has been obtained and the dilator/delivery system is introduced.

Enrollment information (name of the study, date of consent and enrollment criteria, etc.) will be recorded in the hospital records and eCRF. Complete and submit the screening eCRF in a timely manner (recommended within 5 days). Notification of enrollment to the sponsor will take place only when the sponsor receives the Screening eCRF form.

The following terms will be used to describe potential study participants who do not fully implement the study:

- **Consented Screen Failure** - Subjects who sign the Informed Consent Form but do not meet the eligibility criteria. These subjects will not be considered enrolled in the study. Document the enrollment information (name of the study, date of consent and enrollment criteria, etc.) in the hospital records; complete the Screening form.
- **Enrolled Subject – Unsuccessful implant** - Subjects are enrolled but the device was not implanted. The subject will be withdrawn 7 days after procedure. Document the enrollment information (name of the study, date of consent and enrollment criteria, etc.) in the hospital records; The Baseline, Screening, Procedure, Out of service and Withdrawal eCRFs should be completed (withdrawal should occur at least 7 days after the attempted procedure).

Adverse events will be reported from the time the dilator/device delivery system has been introduced to the time the subject concludes the study. An Adverse Event eCRF should be completed, as applicable.

7.2 IMPLANT/PROCEDURE/PRE-DISCHARGE

After it is verified that the subject meets preliminary study enrollment criteria, the implant procedure can be scheduled.
The procedure TEE can serve as the baseline TEE to rule out the presence of intracardiac thrombus (including left atrial appendage thrombus) and to assess size and shape of the LAA.
See the IFU for procedural and post-procedural instructions (refer also to **Table 2**).

7.3 SCHEDULED FOLLOW-UPS

Scheduled office visits occur at 45 days (+45 days), 6M (+/- 3 weeks) 12M (+/- 6 weeks) and 24 M (+/- 6 weeks) post procedure;
Phone contact follow up visits occur at, 36M (+/- 6 weeks), 48M (+/- 6 weeks) and 60 M (+/- 6 weeks) post procedures.
Refer to Table 2 for required follow-up testing and assessments.

7.4 INTERIM/UNSCHEDULED VISITS

Interim/unscheduled visits will be considered those that occur in addition to the required visit interval schedule. If an unscheduled or interim visit occurs, an adverse event assessments eCRF or deviation form, as applicable should be completed to capture data collected at the visit. In the event of a confirmed stroke or TIA, TEE should be conducted within 14 days from the date the site becomes aware of the event and the modified Rankin Scale eCRF should be completed 90 days after the event.

7.5 DESCRIPTION OF ACTIVITIES PERFORMED BY SPONSOR REPRESENTATIVES

Trained Sponsor personnel may perform certain study activities to ensure compliance to the clinical protocol. Monitoring may be performed by SJM and/or authorized designees according to the CFDA regulations, the monitoring plan and applicable SJM standard operating procedures and work instructions. Qualified monitors will ensure investigators comply with this clinical protocol and CFDA regulations.
To ensure study personnel accept, understand and complete their assigned responsibilities, monitors, field clinical personnel, and/or clinical country managers, may perform periodic site visits during the course of the study. These actions will help to ensure the continued acceptability of the facilities, compliance to the clinical protocol and relevant regulations, and the maintenance of complete records. Monitoring will include review and resolution of missing or inconsistent results and source document verification (i.e. comparison of submitted study results to original reports) to assure the accuracy of the reported data.
Sponsor representatives will periodically request source documents, resolution of discrepancies, submission of echocardiography imaging etc. for data cleaning and reporting purposes.

7.6 SUBJECT STUDY COMPLETION

Subjects will complete their participation in the study at the 5-year follow-up visits and will return to receiving medical care per their physician's recommendations.

7.7 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Withdraw subjects who have an unsuccessful implant 7 days after the date of the attempted procedure.
- Subject is deceased (cause must be documented)
- Subject's non-compliance
- Subject is 'lost to follow up': Subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study. (This does not apply to missed visits).
  Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:
  1. A subject will be considered 'Lost to Follow Up' after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's study charts and/or medical record.
  2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the subject's study charts and/or medical record.

Note: If a subject misses one or more of the scheduled follow up visits (inclusive of the assigned visit windows), this will be considered as a missed visit. The subject may therefore still return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal, on a Withdrawal CRF.

When subject withdrawal from the clinical study is due to an adverse event the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

8.0 COMPLIANCE TO CIP

8.1 STATEMENTS OF COMPLIANCE

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki and CFDA regulations and will be compliant to this International Standard and CFDA regulations, as appropriate.

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and authorization from the sponsor in writing for the study. The subject must sign the study informed consent form prior to implant procedure.
If additional requirements are imposed by the IRB/EC or CFDA, those requirements will be followed, if appropriate. If any action is taken by an IRB/EC, and regulatory requirements with respect to the study, that information will be forwarded to St. Jude Medical.

As the sponsor, St. Jude Medical has taken up local insurance policy in accordance with the requirements of the applicable local laws. Appropriate country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, such information will be incorporated into the informed consent, as applicable

8.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

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

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

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

It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form. The site will submit the CRF to St. Jude Medical.

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

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

To obtain approval, the Principal Investigator may call or email and discuss the potential deviation with St. Jude Medical or designee prior to initiating any changes.

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

8.3 REPEATED AND SERIOUS NON-COMPLIANCE

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

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

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

9.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT, DEVICE DEFICIENCY

9.1 DEFINITIONS

9.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under study.

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

9.1.2 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR

- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

9.1.3 Adverse Device Effect (ADE)

An adverse event related to the use of the device.

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

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

9.1.4 Serious Adverse Device Effect (SADE)

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

9.2 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS

Safety surveillance within this study and the safety reporting performed both by the investigator and Sponsor starts as soon as the procedure begins, which is defined as the time the dilator/device delivery system has been introduced into the body. The safety surveillance and the safety reporting will continue until the last visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study.

For the purposes of this study, the following AEs will be collected:

- All AEs (regardless of seriousness)
- All SAEs (regardless of relatedness)
- In addition, the following event types will also be reported
- device embolization, device erosion, clinically significant device interference with surrounding structure, device thrombus, device fracture, device infection (endocarditis / pericarditis), device perforation, device laceration, or device allergy

All AE data will be collected throughout the clinical study and will be reported to the Sponsor through the EDC system. The Investigator will record all AE on the appropriate eCRF as soon as possible, but no later than 5 working days of first learning of the event.

For any SAE (including deaths) and any SADE, the investigator shall notify the Sponsor through the EDC system immediately (but no later than 3 working days) of the investigator's awareness of the event and provide the Sponsor with all necessary documentation needed. The Sponsor will notify relevant regulatory authorities and all the other participating sites no later than 5 working days after awareness of the event.

The investigator and Institution will report SAE (including deaths) and SADE to the IRB/EC / relevant regulatory authorities no later than 24 hours of first learning of the event per CFDA's regulations.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

Adverse events will be monitored by the investigator until they are adequately resolved. The status of the subject's condition should be documented at each follow-up visit.

All adverse events will be reported as per applicable regulatory requirements.

9.3 SUBJECT DEATH

9.3.1 Procedure for recording and reporting subject death

All subject deaths with all necessary documentation needed are to be reported to the Sponsor immediately upon the investigator's awareness of the event. An Adverse Event eCRF should be completed and include additional detail surrounding the death and cause of death. The principal investigator should also record any observed device deficiencies, that may be applicable.

9.4 DEVICE DEFICIENCY (DD)/COMPLAINTS

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

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

Device deficiencies will be reported per country reporting timeline requirements to the Sponsor and are recorded outside of the study database through the EPIQ Complaint system or on a Product Event Report Form.

If the device deficiency involves an adverse event as described in the protocol, the Investigator shall notify the Sponsor by completing the AE form through EDC as applicable and must provide the Sponsor with all necessary documentation needed.

If the device deficiency does not involve a reportable AE per protocol, the Investigator should notify the SJM Product Surveillance Department by submitting the information about the device deficiency to the local country office or to: Complaints_amplatzer@sjm.com or calling +1 651-756-5400 as soon as possible after becoming aware of the device deficiency. Please contact the local SJM representative to coordinate product returns as applicable.

10.0 DATA MANAGEMENT

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

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

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of China and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information collected or maintained for this clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

Electronic CRFs will be used in this study, as noted below and in the data management plan. Informed consent documents will be translated to Chinese, as applicable. If additional documentation is required for any reason (e.g. procedural notes for an adverse event), it is to be appropriately redacted/de-identified prior to being sent to SJM. Source documents will be collected and translated, as needed, for reporting, etc.

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

10.1 DATA MANAGEMENT PLAN

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

CRF data will be captured in a validated electronic database management system hosted by St. Jude Medical. Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system deployed by St. Jude Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

10.2 DOCUMENT AND DATA CONTROL

10.2.1 Traceability of documents and data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.

10.2.2 Recording data

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

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

The CRFs will be signed and dated (validated eCRF) by the authorized site personnel, as specified in the Data Management Plan.

11.0 MONITORING

It is the responsibility of St. Jude Medical as the sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the St. Jude Medical Clinical Monitoring standard operating procedure.

Prior to beginning the study, St. Jude Medical will contact the investigator or designee to discuss the study and data requirements. A St. Jude Medical monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for monitoring.

12.0 REGULATORY INSPECTIONS

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

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

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

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

13.0 STATISTICAL CONSIDERATIONS

13.1 PRIMARY ENDPOINTS

There are three primary endpoints: two safety endpoints and one effectiveness endpoint.

13.1.1 Primary safety endpoint (Short Term)

The short term safety endpoint is the proportion of subjects who experience an major adverse events (short term occurrence of death, stroke (ischemic or haemorrhagic), systemic embolism, or procedure or device-related complications requiring major cardiovascular or endovascular intervention) 7 days after the procedure.

Hypothesis:

H_0: $p_s \geqslant PG_s$

H_1: $p_s < PG_s$

where p_s is the proportion of subjects undergoing the ACP LAA closure procedure, who experience an acute safety endpoint event. [redacted]

The performance goal, PG_s, in this hypothesis is set at 10%.

[redacted]

Analysis Methods:

The proportion of subjects experiencing a primary safety endpoint, p_s, will be estimated from the binomial model. [redacted]

The performance goal assumes that LAA closure occurs in isolation of other cardiac procedures. If the short-term primary safety endpoint is not met, then an additional analysis may be performed excluding subjects who had a cardiac ablation performed in combination with the ACP LAA closure procedure. Excluding subjects who had a cardiac ablation performed in combination with the LAA closure procedure may result in a substantially smaller sample size to evaluate this endpoint; therefore, in this additional analysis, the point estimate for the short-term primary safety endpoint will be descriptively compared to the performance goal, PG_s.

Sample Size Determination:

Sample sizes are calculated assuming an event rate of 5%. The sample size required to reject the null hypothesis with 80% power at the 2.5% significance level is 231 subjects.

Analysis Population:

Enrolled subjects will be included in this analysis.

13.1.2 Primary safety endpoint (Long-Term)

The long-term safety endpoint is the 2-year occurrence of device embolization, device erosion, clinically significant device interference with surrounding structure, device thrombus, device fracture, device infection (endocarditis / pericarditis), device perforation, device laceration, or device allergy.

Hypothesis:

H_0: $p_l \geqslant PG_l$
H_1: $p_l < PG_l$

where p_l is the long-term safety endpoint event rate. It is assumed that the long-term safety endpoint event rate is 5%. [redacted] An event rate of 5% is assumed for the long-term safety endpoint for the ACP device [redacted] The performance goal, PG_l, is set at 10% [redacted]

[redacted]

Analysis Methods:

Kaplan-Meier survival analysis will be used to estimate the event rate of at 24 months (731 days post implant). [redacted]

Sample Size Determination:

The sample size is estimated assuming an event rate of 5%. A sample size of 231 subjects followed through 24 months will provide 80% power at the 2.5% significance level. Assuming an attrition rate of 25% through 24 months, 308 subjects are required to be enrolled in the study.

Analysis Population:

Enrolled subjects will be included in this analysis.

13.1.3 Primary effectiveness endpoint:

The primary effectiveness endpoint is the composite endpoint of ischemic stroke or systemic embolism at 2 years.

Hypothesis:

H_0: $p_e \geqslant PG_e$
H_1: $p_e < PG_e$

where p_e is the event rate at 24 months. [redacted] The performance goal, PG_e is set at 9%, [redacted]

[redacted]

Analysis Methods:

[redacted]

[redacted]

Kaplan-Meier survival analysis will be used to estimate the event rate of at 24 months (731 days post implant). [redacted]

Sample Size Determination:

A sample size of 257 subjects followed through 24 months will provide 80% power at the 2.5% significance level assuming a 24-month event rate of 4.5%. Assuming an attrition rate of 25% through 24 months, 343 subjects are required to be enrolled in the study.

Analysis Population:

Enrolled subjects who receive an implant of the ACP device will be included in the analysis.

13.2 DESCRIPTIVE ENDPOINTS

The following endpoints will be summarized using descriptive statistics.

Rate of ischemic stroke or systemic embolism through 5 years post-implant:

Kaplan-Meier survival analysis will be used to estimate the rate of ischemic stroke or systemic embolism through 5 years post-implant. Subjects who receive an implant of the ACP device will be included in the analysis.

Occurrence of composite of damage to blood vessel or organ or damage to adjacent organs at implant, device dislodgement, device fracture, device erosion or pericardial tamponade through 5 years post-procedure :

Kaplan-Meier survival analysis will be used to estimate the rate of occurrence of the composite of device dislodgement, device fracture, device erosion, pericardial tamponade, damage to blood vessel or organ at implant access or damage to adjacent organs through 5 years post procedure. Subjects who receive an implant of the ACP device will be included in the analysis.

Device success rate- defined as device deployed and implanted in correct position:

The count and proportion of subject with device success will be summarized. Subjects who receive an implant of the ACP device will be included in the analysis.

Rate of closure of the LAA - defined as residual jet around the device of $\leqslant$ 5mm, based on the 45-day TEE:

The count and proportion of subject with closure of the LAA will be summarized. Subjects who receive an implant of the ACP device will be included in the analysis.

Reporting:

The following data will be summarized and reported annually to CFDA.

- Investigator sites and enrollment status
- Demographic and baseline characteristics
- Serious Adverse events
- Protocol deviation

- Procedural results (procedure success, implanted device size, procedure duration)
- Device closure

13.3 SAMPLE SIZE

The overall sample size required for this study is 343 subjects, which is driven by the primary effectiveness endpoint.

[redacted]

13.4 SUCCESS CRITERIA

The study has three primary endpoints for safety and effectiveness. All three endpoints must be met in order to declare success.

13.5 INTERIM ANALYSIS

No interim analyses are planned for this study.

13.6 STATISTICAL CRITERIA FOR TERMINATION

There are no statistical criteria for termination of this study.

13.7 DEVIATIONS FROM STATISTICAL PLAN

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

14.0 DOCUMENT RETENTION

The principal investigator (PI) will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the site for a minimum of 10 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

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

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

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

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

15.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, CIP, eCRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the Sponsor and the coordinating investigator (if applicable).

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

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

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

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

16.0 OUTSOURCING OF DUTIES AND FUNCTIONS (IF APPLICABLE)

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

16.1 PROJECT MANAGEMENT

The project management of this study will be performed by Abbott on behalf of St. Jude Medical Coordination Center BVBA:

[redacted]

17.0 INVESTIGATION SUSPENSION OR TERMINATION

17.1 PREMATURE TERMINATION OF THE WHOLE CLINICAL STUDY OR OF THE CLINICAL STUDY IN ONE OR MORE INVESTIGATIONAL SITES

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

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

- The device / therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision
- Recommendation from DSMB to Steering committee and Sponsor
- Request from Regulatory bodies
- Request of Ethics Committee(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse device effects within 72 hours to St. Jude Medical and the EC
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

The study will be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor.

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

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

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

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

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

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the IRB/EC are notified, either by the Principal Investigator or by St. Jude Medical. If

the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

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

17.2 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

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

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

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

17.3 STUDY CONCLUSION

The study will be concluded when:

- All sites are closed AND
- The Final report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure

18.0 PUBLICATION POLICY

The results of the clinical study are planned to be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

[redacted]

This study will be posted on public database.

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APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CCI	Clinical Coordination Investigator
CIP	Clinical Investigational Plan
CRF	Case Report Form
CPRB	Clinical Project Review Board
DD	Device Deficiency
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
GP	General Practitioner
IB	Investigator Brochure
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISB	Investigator Site Binder
ISO	International Organization for Standardization
MP	Monitoring Plan
NA	Not Applicable
PI	Principal Investigator
POA	Power of Attorney
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

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Appendix C: DECLARATION OF HELSINKI

The 2013 version of the Declaration of Helsinki is available at: http://www.wma.net/en/20activities/10ethics/10helsinki/. Please check the website during the course of the study for updated revisions most current version.

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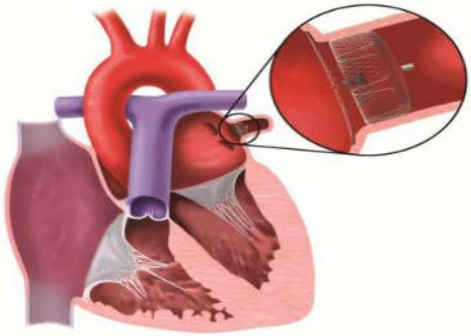

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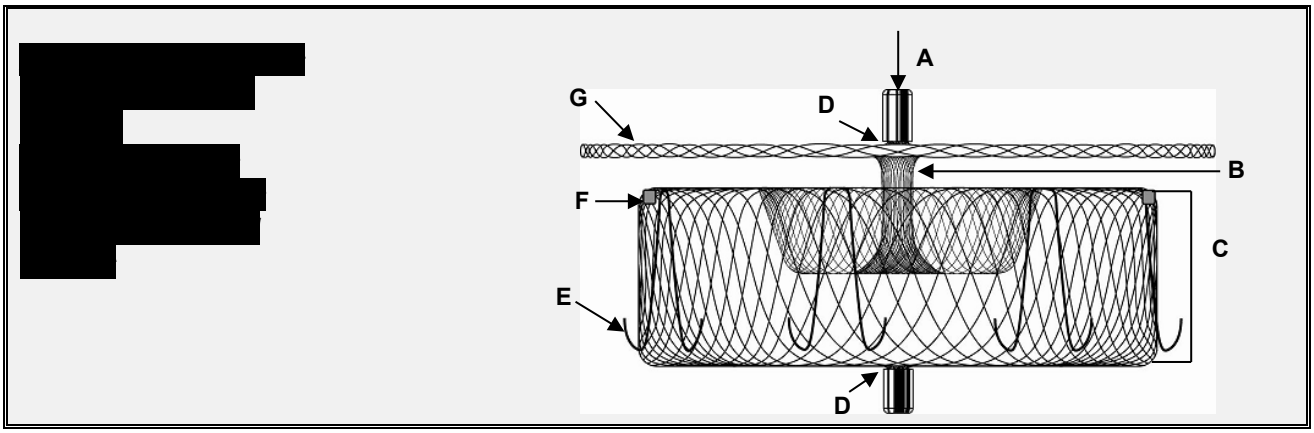

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Appendix G: Definitions of Potential Adverse Event

- **Air Embolus** – symptomatic event resulting from the introduction of air into the circulatory system
- **Allergic reaction** – idiosyncratic reaction to the device implanted or to nickel
- **Anesthesia reaction** – undesired reaction to anesthetic agent
- **Arrhythmia** – cardiac rhythm disturbance
- **Bleeding** –see **Appendix H**
- **Cardiac arrest** – failure of the heart to contract
- **Cardiac tamponade** – constriction of the heart causing inefficient contraction resulting from accumulation of excess fluid in the pericardium
- **Death** – permanent cessation of all vital bodily functions
- **Device embolization** – movement of the device from its intended location
- **Device migration** – movement of the device within its intended location
- **Embolic event** – acute vascular insufficiency or occlusion of the extremities or any non-central nervous system organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion
- **Fever** – defined as a body temperature > 37.5 or 38.3 °C (99.5 or 100.9 °F)[1]
- **Foreign body embolization** – movement of device material, delivery system material, or other material from its intended location
- **Hypotension** – sustained systolic blood pressure < 90 mmHg
- **Hypertension** – systolic blood pressure of > 160 mmHg
- **Infection** – invasion and growth of a pathogenic organism within the body
- **Multi-Organ Failure –** the failure of two or more systems, such as the cardiovascular and renal systems, and is a common consequence of sepsis (the presence of bacteria in the blood) and of shock (very low blood pressure)
- **Myocardial infarction (heart attack)** – the death of heart muscle from the sudden blockage of a coronary artery by a blood clot
- **Perforation** – physical penetration of a vessel or the myocardium
- **Pericardial effusion** – abnormal fluid collection around the heart without hemodynamic compromise
- **Renal failure/dysfunction** – inability of kidneys to perform normal functions
- **Respiratory failure** – inability of the lungs to perform normal functions
- **Seizure** – uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms
- **Significant Residual Flow –** flow > 5 mm jet into the LAA
- **Stroke** – an acute episode (lasting > 24 hours) of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Strokes are characterized as follows[35]:
    - **Ischemic Stroke**: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue. Hemorrhage may be a

consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

- **Hemorrhagic Stroke**: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
- **Undetermined Stroke**: an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic stroke

- **Thrombus Formation** – a blood clot
- **Transient Ischemic Attack** (TIA)– a transient episode (lasting ≤ 24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction on brain imaging
- **Valvular regurgitation/insufficiency** – backflow of blood during contraction of the heart; caused by a defective heart valve
- **Vascular access site injury** – damage at vascular access site (e.g., AV fistula, hematoma, and aneurysm)
- **Vessel Trauma/Injury** – traumatic injuries that damage an artery or vein

Appendix H: Modified Rankin Scale (mRS)

Subject Identifier: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0-6): _____