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MitraClip China Post-Market Study (PMS)
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Sponsor: Abbott Vascular

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MitraClip China Post Market Study Clinical Investigational Plan

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MitraClip China PMS

A Prospective, Multi-Center, Single-Arm, Post Market Study of the MitraClip System for the Treatment of Symptomatic Mitral Regurgitation in China

[redacted]	[redacted]
[redacted]	[redacted]
Planned Number of Sites and Region(s)	Up to 10 sites in China
Trial Type	Post Market Study (PMS)
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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Site Principal Investigator Signature Page

Study Title: MitraClip China PMS: A Prospective, Multi-Center, Single-Arm, Post Market Study of the MitraClip System for the Treatment of Symptomatic Mitral Regurgitation in China

Study Number: CRD956-PMS

[redacted]

I have read and agree to adhere to the MitraClip China Post Market Study (PMS) Clinical Investigational Plan and all regulatory requirements applicable in conducting this study.

Site Principal Investigator

Printed name:
Signature:
Date:

[redacted]

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Compliance Statement:

The MitraClip China PMS Study will be conducted in accordance with this Clinical Investigational Plan, the Declaration of Helsinki and the National Medical Products Administration (NMPA) applicable regulations. The most stringent requirements, guidelines or regulations must always be followed. The conduct of the study will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

This clinical study will be filed in compliance with Regulations on Management of Human Genetic Resources of the People's Republic of China (2019 No. 717) with the Human Genetics Resources Administration of China.

1 INTRODUCTION

Mitral regurgitation (MR) is the most common heart valve condition in the world. MR occurs when the mitral valve does not close properly, allowing blood to leak back into the upper chamber of the heart. As a result, the heart may try to pump harder in order to compensate for the decrease in blood flow to the rest of the body. Patients with severe MR suffer from debilitating symptoms such as shortness of breath, heart palpitations, lightheadedness, and fatigue. These patients are at risk of poor quality of life, marked limitation in activity, repeated heart failure hospitalizations, and increased mortality. Chronic severe MR is often associated with heart failure and can lead to death if left untreated.

While mitral valve repair or replacement surgery is currently regarded as standard of care, many patients with clinically significant MR are at an unacceptable risk of morbidity and mortality and are therefore not appropriate surgical candidates. To optimize afterload reduction and treatment of fluid load, these patients are often treated with medical management (i.e., beta blockers, ACE inhibitors, angiotensin II receptor blockers) which may relieve MR symptoms, but does not address the underlying cause of the condition. As a result, a significant portion of patients treated medically continue to progress to heart failure and experience an increasingly debilitating quality of life. A significant unmet clinical need thus exists for the treatment of moderate-to-severe and severe MR in high surgical risk patients.

The MitraClip® System is the first commercially available catheter-based option for the treatment of MR. The MitraClip System was developed as an alternate percutaneous technology which may serve as a viable therapeutic option for open-heart surgery. Treatment with the MitraClip device allows patients to undergo a less invasive procedure that can mechanistically reduce MR and allow for improved quality of life. The MitraClip procedure is performed under general anesthesia without the use of a heart-lung machine, with recovery typically lasting two to three days.

The MitraClip System has been in clinical use for treatment of significant MR since 2003. The MitraClip System received CE (Conformité Européenne) Mark for both DMR and FMR indications in March 2008 and was approved by FDA for DMR indication in October 2013 and for FMR indication in March 2019. The system is approved for use in more than 102 countries or regions worldwide. More than 100,000 patients have undergone the MitraClip procedure worldwide.

On June 15, 2020, the MitraClip System has been approved [redacted] for clinical use in China.

The MitraClip China PMS will be conducted in accordance with this Clinical Investigational Plan (CIP, protocol). All investigators involved in the conduct of the study will be qualified by education, training, or experience to perform their tasks and this training will documented appropriately.

1.1 Background and Rationale

1.1.1 Background

This section summarizes results of studies in North America and Europe comprising the majority of the MitraClip Clinical Program as well as China and Asia-Pacific experiences. Rationale for the MitraClip China PMS Study is subsequently presented in the context of this scientific body of evidence.

EVEREST I Design and Results

The EVEREST I Feasibility trial was the first prospective, multi-center, non-randomized trial to evaluate the preliminary safety and effectiveness of the percutaneous MitraClip System in patients with moderate-to-severe (3+) or severe (4+) MR in surgical candidates. After undergoing the MitraClip procedure, patients were followed at discharge, 30 days, 6, 12, 18 and 24 months and every year thereafter through 5 years. An independent Echocardiography Core Laboratory (ECL) assessed MR severity and other echocardiographic parameters at baseline and follow-up. The last patient has completed 5-year follow-up and the study is now closed.

A total of 55 patients were enrolled in the trial. The MitraClip device was implanted in 89% of patients and the trial met its pre-specified safety acceptance criterion, demonstrating mechanistic feasibility of implant and safety of the MitraClip System and procedure. There were no intra-procedural deaths. The procedure time averaged approximately 4 hours, patients were hemodynamically stable during the procedure, and the average length of hospital stay was approximately 3 days. A majority of patients (70.9%) experienced reduction in MR severity to 2+ or less at discharge. No MitraClip device embolization occurred in this cohort. The rate of single leaflet device attachment (SLDA) in this initial cohort of patients treated was 10.2%. A majority of SLDAs were detected early (within 30 days post-MitraClip procedure). Patients demonstrated improvement in NYHA Functional Class and left ventricular measurements that were sustained through 5 years. At 5 years, freedom from death was 86.4% and freedom from mitral valve surgery was 55.1%. The results of the EVEREST I trial at 5 years provide evidence of the safety and long-term durability of the MitraClip device in the early cohort of patients treated in the United States.

EVEREST II Randomized Controlled Trial (RCT) Design and Results

The EVEREST II RCT is a prospective, multi-center, randomized controlled trial in which patients with moderate-to-severe (3+) or severe (4+) MR were randomized in a 2:1 ratio between the Device group (MitraClip device) and the Control group (mitral valve surgery). Patient follow-up occurred at discharge, 30 days, 6, 12, 18 and 24 months and yearly thereafter through 5 years. An independent Echocardiography Core Laboratory (ECL) assessed MR severity and other echocardiographic parameters at baseline and follow-up. The trial was intended to demonstrate superiority of safety balanced against reduced effectiveness of the MitraClip device when compared to mitral valve surgery. All patients have completed 5 years of follow-up and the study is now closed.

The trial enrolled 279 patients: 184 in the Device group and 95 in the Control group. Of these, 178 patients in the Device group underwent the MitraClip procedure and 80 patients

[redacted]

in the Control group underwent mitral valve surgery. The trial met both primary safety and effectiveness endpoints. There were no intra-procedural deaths. Among patients who underwent the MitraClip procedure in the Device group (MitraClip patients), a device was implanted in 89% of patients. The procedure time averaged approximately 3 hours, patients were hemodynamically stable during the procedure, and the average length of hospital stay was less than 3 days. In comparison, the average length of hospital stay for patients undergoing surgery in the Control group (surgery patients) was 7.5 days. A large majority (94.9%) of MitraClip patients were discharged home without home healthcare. In comparison, 71.3% of surgery patients were discharged home without home healthcare. A majority of MitraClip device patients (77%) experienced reduction in MR severity to 2+ or less at discharge, while 100% of patients undergoing mitral valve surgery in the Control group experienced reduction in MR severity to 2+ or less.

Patients who underwent the MitraClip procedure experienced a 30-day major adverse event rate (composite of death, myocardial infarction (MI), re-operation for failed surgical repair or replacement, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, ventilation for greater than 48 hours, GI complication requiring surgery, new onset of permanent atrial fibrillation, septicemia and major bleeding complication) of 7.9% versus 50% in patients who underwent mitral valve surgery in the Control group. Excluding the most common event of major bleeding complication, MitraClip device patients still experienced a lower major adverse event rate (4.5%) than surgery patients (11.3%) (p=0.057).

Through 30 days, MitraClip patients experienced a lower site-reported adverse event rate than surgery patients in the following categories: cardiac rhythm disorders (atrial arrhythmias, bradyarrhythmia, and ventricular arrhythmias), congestive heart failure, peripheral edema, anemia, infections, neurologic events and respiratory events. At 30 days, MitraClip patients experienced a higher event rate than surgery patients in the following categories: atrial septal defect, myocardial ischemia, residual or recurrent MR, single leaflet device attachment (SLDA), gastrointestinal bleed, and vascular complications such as hematoma, bleed or bruising.

Beyond 30 days through 5 years, site-reported adverse events occurred at a low rate in both MitraClip and surgery patients and there was no signal for an elevated adverse event rate in either group.

Through 5 years, there was only one confirmed case of mitral stenosis (0.6%) reported in patients implanted with the MitraClip device. Through 5 years, no MitraClip device embolization has occurred. SLDAs occurred at a lower rate (6.3%) than that observed in the EVEREST I trial (10.2%). A majority of the SLDAs were detected early (within 30 days post-MitraClip procedure).

There was no difference in mortality rates between patients treated in either group during the entire 5-year follow-up period. Freedom from mortality at 12 months, 24 months, 3 years, 4 years and 5 years was 93.7%, 90.0%, 87.5%, 83.4% and 81.2% respectively in MitraClip patients, and 92.3%, 89.6%, 85.3%, 82.3%, and 79.0%, respectively in surgery patients.

Therefore at 5 years, the MitraClip device continues to demonstrate a favorable safety profile and does not present any long-term safety concerns.

Freedom from mitral valve surgery in MitraClip patients at 12 months, 24 months, 3 years, 4 years, and 5 years was 78.9%, 78.2%, 77.6%, 76.0%, and 74.3%, respectively, and freedom from re-operation in surgery patients was 97.4%, 96.0%, 94.4%, 94.4%, and 92.5%, respectively. Weibull estimates of freedom from death, mitral valve surgery and MR > 2+ at 12 months, 24 months, 3 years, and 4 years was 60.8%, 55.4%, 52.0%, and 49.5%, respectively, in MitraClip patients; and freedom from death, re-operation and MR >2+ was 89.0%, 82.6%, 77.6%, and 73.3%, respectively, in surgery patients. While there was an initial drop in freedom from death, mitral valve surgery and MR > 2+ due to MitraClip patients undergoing mitral valve surgery within 12 months of the MitraClip procedure, these patients did not experience any worse deterioration in durability than surgery patients beyond 12 months.

Significant and meaningful clinical benefits were observed in both MitraClip and surgery patients, which were sustained through 5 years:

- MR reduction to 2+ or less at 5 years was in 82.1% of MitraClip patients and 97.6% of surgery patients
- Reduction in left ventricular end diastolic volume and dimension was observed in both MitraClip and surgery patients, which was sustained through 5 years
- Improvement in NYHA Functional Class was demonstrated in both groups, with 91.5% of MitraClip patients and 97.6% of surgery patients free from NYHA Functional Class III or IV symptoms at 5 years

The results of the EVEREST II RCT demonstrate the continued safety, durability of effectiveness and clinical benefit of the MitraClip device through 5 years. These results are consistent with the expectation of superior safety and reduced effectiveness of the MitraClip device when compared to mitral valve surgery. These results support an overall favorable risk to benefit profile of the MitraClip device through 5 years.

<u>EVEREST II High Risk Registry Design and Results</u>

The EVEREST II High Risk Registry is a single-arm prospective, multi-center clinical trial enrolling high surgical risk patients with moderate-to-severe (3+) or severe (4+) MR. Patients were considered high surgical risk if either their Society of Thoracic Surgery (STS) predicted operative mortality risk was ≥ 12%, or the surgeon investigator determined the patient to be high risk due to the presence of pre-specified risk factors. After undergoing the MitraClip procedure, patients were followed at discharge, 30 days, 6, 12, 18 and 24 months and yearly thereafter through 5 years. All patients have completed the required 5 years of follow-up and the study is now closed. An independent Echocardiography Core Laboratory (ECL) assessed MR severity and other echocardiographic parameters at baseline and follow-up.

A total of 78 patients were enrolled in the EVEREST II High Risk Registry. The device was implanted in 96.2% of patients. There were no intra-procedural deaths. The procedure

time averaged approximately 3 hours, patients were hemodynamically stable during the procedure, and the average length of hospital stay was less than 4 days. A majority (75.6%) of these high surgical risk patients were discharged home without home healthcare. A majority of patients (71.8%) experienced reduction in MR severity to 2+ or less at discharge post-MitraClip procedure.

The 30-day operative mortality for mitral valve replacement (using STS version 2.52) was 7.7%, which was statistically significantly lower than the predicted surgical mortality. The trial thus met the pre-specified primary safety endpoint. This rate was comparable to the observed mortality at 30 days in the Concurrent Control (8.3%). Major adverse events at 30 days occurred at a rate (26.9%) consistent with their co-morbidities, with transfusions ≥ 2 units of blood contributing the majority of events. At 12 months, freedom from death in the High Risk Registry patients was higher (75.4%) than that observed in the Concurrent Control (55.3%). SLDAs occurred at a low rate (1.3%).

MR reduction to 2+ or less in this high surgical risk population was sustained in 75.0% of patients through 5 years. For this high surgical risk population with limited options to treat MR, safe reduction of MR is clinically meaningful, as observed in the following endpoints:

- 45% reduction in the 12-month rate of hospitalization for heart failure post-treatment compare with the 12-month rate prior to MitraClip intervention
- Reduction in left ventricular end diastolic volume and dimension, and left ventricular end systolic volume, which was sustained through 5 years
- NYHA Functional Class was improved from approximately 90% of patients in NYHA Functional Class III or IV at baseline to 83.7% free from NYHA Functional Class III or IV symptoms at 5 years

The results of the EVEREST II High Risk Registry demonstrate continued safety, durability of effectiveness and clinical benefit of the MitraClip device through 5 years. These results support an overall favorable risk to benefit profile of the MitraClip device in high surgical risk patients through 5 years.

<u>EVEREST II REALISM Study Design and Results</u>

The objective of the EVEREST II REALISM Continued Access Registry was to collect data on the use of the minimally-invasive catheter-based MitraClip device under “real-world” conditions in high risk and non-high risk patients with moderate-to-severe (3+) or severe (4+) chronic MR. REALISM was a prospective, multi-center, Continued Access Registry. The study enrolled patients in two arms: the high risk and non-high risk arms. Eligibility for the Non-High Risk arm was the same as for the EVEREST II RCT and that for the High Risk arm was the same as for the HRR.

Enrollment in the Continued Access REALISM study was initiated on January 22, 2009. A total of 899 patients (628 High Risk, 271 Non-High Risk) were enrolled and treated in the EVEREST II REALISM Continued Access Study. Enrollment in the Non-High Risk arm of

the study concluded on April 14, 2011 and enrollment in the High Risk arm concluded on December 19, 2013.

All-cause mortality and major adverse event rates at 30 days in the REALISM High Risk arms were 4.1% and 15.6% respectively. The 12 months all-cause mortality and major adverse event rates were 23.4% and 35.5% respectively.

The severity of MR consistently remained mild to moderate (2+ or less) for a majority (>80%) of the patients and the NYHA Functional Class were Class I/II for a majority (>80%) of the patients through 5 years.

The safety and durability results of the REALISM High Risk arms provide further evidence that the "real-world" use of the MitraClip device continues to perform as expected based on the EVEREST II Randomized Controlled Trial and High Risk Registry.

MitraClip Experiences in Chinese and Asian-Pacific Population

Early experience of the MitraClip device in China has been reported.[1] Of the 3 cases reported, two patients had FMR and one patient had DMR. In all 3 cases, the MitraClip device was successful implanted. In the first two cases, follow up was completed through 6-month with no adverse events reported. Discharge echocardiography showed significant reduction in MR, decreases in left atrial and left ventricular inner diameters, decreases in systolic pulmonary artery pressure, and NYHA class improvement when compared to baseline. These results were maintained through 6 months. In the third patient, MR was significantly reduced from discharge to 1 month. After month two, however, the patient's MR increased, left atrium and ventricle were further enlarged, cardiac function further deteriorated, even though multiple echocardiography results showed that the MitraClip device was still attached well. After treatment with aggressive heart failure medications, the patient died 162 days post implant due to heart failure and cardiogenic shock.

Additionally, Liu et al reported a single center experience with the MitraClip device.[2] A total of 10 patients were treated with the MitraClip device, including eight patients treated with FMR and two patients treated with DMR. The mean age was 74 years. The procedure success was 100%. Five patients were implanted with one MitraClip device and the remaining 5 patients had 2 MitraClip devices implanted. Acute MR reduction by 3 grades was achieved in 5 patients and by 2 grades in the other 5 patients. Thirty-day follow-up results demonstrated significant improvements from baseline in MR grade (3.9 vs. 1.7), LVEF (40.2% vs. 44.8%), quality of life measures (0.7 vs. 0.9), 6-minute walk test (279 vs. 344 m), NYHA class (2.9 vs. 2.1), left atrium end diastolic dimension (6.4 vs. 6.0 cm), and left ventricle end diastolic dimension (6.1 vs. 6.0 cm). There was no mitral valve surgery due to MitraClip failure, myocardial infarction, death, MitraClip detachment, thromboembolization, MV damage, mitral stenosis, tamponade, stroke or newly occurred atrial fibrillation observed in the study. The study concluded that the initial experience with intravascular mitral valve repair using the MitraClip system demonstrated that the procedure was safe and effective, resulting in substantial echocardiographic and early clinical improvement. The long-term benefit of MitraClip should be validated through follow-up.

Most recently, Lee et al. published their results of MitraClip performance in Chinese population.[3] They enrolled a total of 20 patients with heart failure and severe MR, including DMR (55%), FMR (40%) and mixed (5%). The mean age of the cohort was 75 years. Among the 20 procedures, 4 were performed emergently while the patients were on mechanical hemodynamic support or inotropic agents. On average, 1.8 clips were implanted in this cohort and the acute procedure success was 95%. There was no peri-procedure death, MI, stroke or any adverse events requiring emergent cardiac surgery. One patient died within 30 days post procedure due to deteriorating hyperbilirubinemia when MR was not successfully abolished. The 30-day mortality was 5%. Thirty-day follow-up results showed MR was significantly reduced (1+: 70%, 2+: 20%, 3+: 5%) compared to baseline (4+: 100%). Patient's functional status was also significantly improved. All patients were with NYHA class I or II at 30 days post procedure; the six-minute walk distance increased from 219.6 to 279.1 meters (p = 0.04). The study concluded that trans-catheter edge-to-edge mitral valve repairs are safe and effective in Asians with symptomatic MR, regarding the improvements of clinical symptoms and exercise capacities.

In addition, a MitraClip Asia-Pacific Registry (MARS) was conducted by eight study sites in five Asia-Pacific countries, including Zhejiang University School of Medicine, Hanzhou, China.[4] The objective of the registry was to describe and compare the used of the MitraClip therapy in DMR and FMR. As reported, acute procedure success rates for FMR and DMR were similar (95.5% vs. 92%, p=0.515). The 30-day mortality and MAE rates were 4.5% vs. 6.7% (p=0.555) and 9.2% vs. 14.7% (p=0.281) for FMR and DMR respectively. In both FMR and DMR patients, there was marked improvement of the severity of MR 30-day post-procedure. The percent of patient with NYHA class I-II was increased from 21.6% vs. 38.7% to 78.9% vs. 78.2% at 30-day post implant for FMR and DMR respectively. Hemodynamically, the mean mitral valve pressure gradient was 3.7 vs. 4.0 mmHg and MR ≥ 2+ was reduced to 10.7% vs. 14.3% at 30-day follow-up for FMR and DMR respectively. For FMR, there was a significant reduction in LVEDD, LA indexed volume and PASP at 30 days. For DMR, LVEDD and LVESD were significantly reduced. In this study, it was concluded that the MitraClip device is a safe and effective option for patients with both FMR and DMR.

1.1.2 Rationale for Conducting this Post Market Study

The safety and efficacy of MitraClip have been demonstrated in these patients in U.S. clinical studies such as EVEREST II HRR trial and EVEREST II REALISM HRR trial, described above. The data also showed the safety and efficacy of MitraClip in Chinese and other Asia-Pacific patients. Per National Medical Products Administration (NMPA) post approval request, the MitraClip China PMS is planned to confirm the evidence of safety and efficacy of MitraClip System in Chinese subjects with symptomatic MR. Upon completion of the study, a study report will be submitted to fulfill NMPA post approval requirement.

2 STUDY OVERVIEW

2.1 Study Objective

To confirm the evidence of safety and efficacy of MitraClip System in Chinese symptomatic MR subjects with a post market setting.

2.2 Device used in the Study

2.2.1 Name of the Device

Device to be used in the MitraClip China PMS is the MitraClip system [redacted].

2.2.2 Indication for Use

MitraClip procedures for this study will be conducted in accordance with the Instructions for Use (IFU) approved by NMPA.

2.2.3 Description of the Device

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3 STUDY DESIGN

The MitraClip China PMS is a prospective, multi-center, single-arm, post market study designed to collect data on use of the MitraClip System in Chinese subjects. A minimum of 50 subjects and a maximum of approximately 100 will be registered up to 10 sites in the MitraClip China PMS. Follow-up of subjects registered in the MitraClip China PMS will occur at discharge, 30 days and 1 year. [redacted]

3.1 Study Procedure and Follow-up Schedule

Figure 1 shows an overall flow of the study. Subjects will be screened for study eligibility by the Investigator as well as the local Site Heart Team per the inclusion and exclusion criteria. A cardiac surgeon and an echo specialist assess subjects for eligibility criteria for surgical risks and echocardiography, respectively.

[redacted]

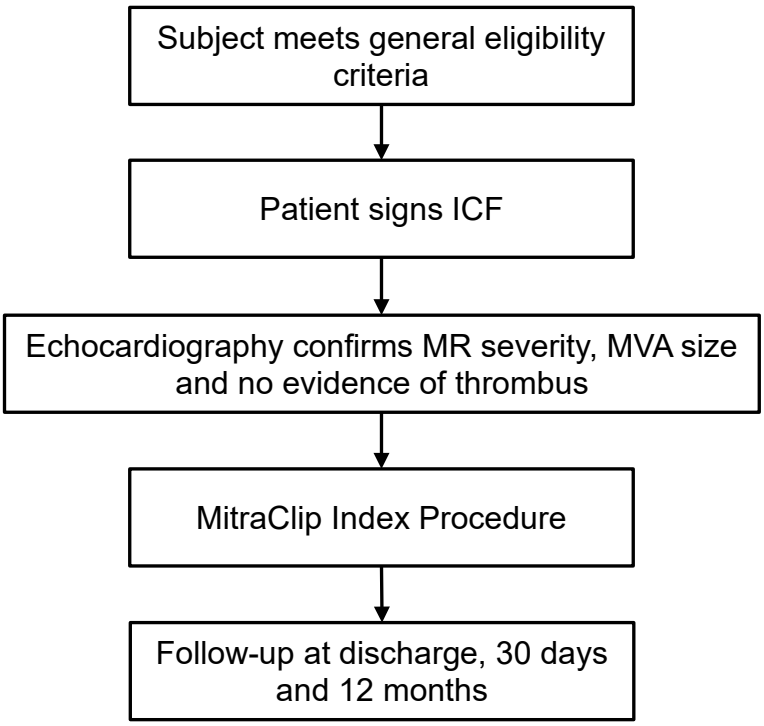

Figure 1: Study Flow Chart

3.2 Measures Taken to Avoid and Minimize Bias

The following steps will be taken to minimize bias:

- Study sites will attempt to recruit consecutive subjects who meet the study eligibility criteria
- Baseline and follow-up echocardiographic parameters will be confirmed by an independent Echocardiography Core Laboratory
- Standardized scripts will be implemented at study sites for the assessment of NYHA classification, and Kansas City Cardiomyopathy Questionnaire (KCCQ)

3.3 Early Termination of the Study

While no formal statistical rule for early termination of the study is defined, the Sponsor reserves the right to discontinue the study at any stage or reduce the follow-up period with suitable written notice to the investigator.

Should the Sponsor discontinue the study, sites will follow subjects per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall provide a written statement to the EC (if applicable). All applicable study documents shall be subject to the same retention policy as detailed in **Section 11.5** of the protocol.

[redacted]

If the Sponsor suspends or prematurely terminates the clinical study at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators and ECs.

If suspension or premature termination occurs, the Principal Investigator or authorized designee will promptly inform the registered subjects at his/her site, if appropriate, and return patients to their standard medical treatment.

A Principal Investigator, EC, or regulatory authority may also suspend or prematurely terminate participation in the clinical study at the site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If a suspended study is to be resumed, a prior approval should be obtained from the EC and a notification should be sent to the regulatory bodies.

4 ENDPOINTS

4.1 Primary Endpoints

Two primary endpoints are designed for the MitraClip China PMS.

- Acute procedural success (APS). APS is defined as successful implantation of the MitraClip device(s) with resulting MR severity of 2+ or less as determined by the ECL assessment of a discharge echocardiogram (30-day echocardiogram will be used if discharge echocardiogram is unavailable or uninterpretable). Patients who die or who undergo mitral valve surgery before discharge are an APS failure.
- Freedom from major adverse event (MAE) at 30 days. MAE is a composite of death, stroke, MI, renal failure, and non-elective cardiovascular surgery for device or procedure related adverse events occurring after the femoral vein puncture for transseptal access.

4.2 Descriptive Endpoints

Clinical Endpoints

The following descriptive clinical endpoints will be assessed at all scheduled office visits.

- All-cause mortality
- Freedom from the components of MAE
- NYHA Functional Class
- Kansas City Cardiomyopathy Questionnaire (KCCQ) Quality of Life (QoL) scores
- Six Minute Walk Test (6MWT) distance
- Mitral valve surgery (including type of surgery), including reason for intervention

- Additional MitraClip System intervention, including reason for intervention
- Number of hospitalizations and reason for hospitalization (i.e. heart failure, cardiovascular, non-cardiovascular)
- Device-related complications: defined as a composite of single leaflet device attachment (SLDA), device embolization, clinically significant iatrogenic septal defect or mitral stenosis that requires intervention.
- Major bleeding

Device and Procedure-Related Endpoints

- Total Procedure Time: defined as the time elapsed from the first of any of the following: intravascular catheter placement, anesthesia or sedation, or transesophageal echocardiogram (TEE), to the removal of the last catheter and TEE
- Device Procedure Time: Defined as the time elapsed from the start of the transseptal procedure to the time the Steerable Guide Catheter is removed
- Device Time: Defined as the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System is retracted into the Steerable Guide Catheter
- Fluoroscopy Time: defined as the total minutes of exposure to fluoroscopy during the MitraClip procedure
- Length of stay in Intensive Care Unit/Critical Care Unit/Post-Anesthesia Care Unit (ICU/CCU/PACU)
- Length of hospital stay for index MitraClip procedure

Echocardiographic Endpoints

The following descriptive echocardiographic endpoints will be assessed at all scheduled office visits.

- MR Severity Grade
- Effective Regurgitant Orifice Area
- Regurgitant Volume (RV)
- Regurgitant Fraction (RF)
- Left Ventricular End Diastolic Volume (LVEDV)
- Left Ventricular End Systolic Volume (LVESV)
- Left Ventricular End Diastolic Dimension (LVEDD)
- Left Ventricular End Systolic Dimension (LVESD)
- Left Ventricular Ejection Fraction (LVEF)

[redacted]

- Right Ventricular Systolic Pressure (RVSP)
- Mitral Valve Area (MVA)
- Mean Mitral Valve Pressure Gradient (MVG)
- Systolic Anterior Motion of the mitral valve (present or absent)
- Forward Stroke Volume (FSV)
- Cardiac Output (CO)
- Cardiac Index (CI)

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

The MitraClip China PMS will enroll and registered male and female Chinese subjects with symptomatic MR who satisfy the inclusion and exclusion criteria and who are treated with the MitraClip System. Subjects must provide written informed consent to participate the study prior to conducting MitraClip procedure.

5.2 Subject Recruitment/Screening and Informed Consent

5.2.1 Subject Recruitment and Screening

The Principal Investigator at the site has the overall responsibility for recruitment and screening subjects for the MitraClip China PMS. Subjects must be screened for general eligibility by a delegated member of the site's study team previously trained to the PMS protocol.

A patient who does not satisfy all general eligibility criteria prior to informed consent is considered a recruitment failure and should not be enrolled in the study.

Potential subjects presenting at the clinical sites who meet general inclusion criteria and no general exclusion criteria will be fully informed about the MitraClip China PMS, following the established Informed Consent process described in section below. Once a duly dated and signed Informed Consent form (ICF) is obtained, the study-specific screening procedure may begin.

Subjects who do not meet the study screening criteria are considered a screen failure and should be withdrawn from the study. The Principal Investigator or the delegated study personnel will record the screen failure in the hospital records and on a recruitment/screening log as required.

All subjects who are found to meet all inclusion and no exclusion criteria must have a documented in-person consultation with the Cardiothoracic (CT) Surgeon investigator to assess surgical risk. The MitraClip implanter (who may also be the Principal Investigator)

and a physician trained in echocardiography will also assess anatomic suitability of the subject for eligibility in the study.

The responsibilities of the various roles/specialties on the local site heart team are summarized below:

Role / Specialty	Responsibility
Interventional Cardiologist	1. Local Site Heart Team Member 2. Screens potential subjects 3. Performs MitraClip procedure*
CT Surgeon	1. Local Site Heart Team Member 2. Provides in-person assessment of surgical difficulty
Echocardiographer	1. Local Site Heart Team Member 2. Evaluates potential subjects for echocardiographic eligibility criteria 3. Participates in the MitraClip procedure

** The MitraClip Implanter can be Interventional Cardiologist, CT Surgeon, or Echocardiographer provided that he/she has completed the mandatory MitraClip Therapy Training and is authorized by the Sponsor and the Principal Investigator to perform the MitraClip procedure*

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's EC. This process will include a verbal discussion with the patient on all aspects of the study that are relevant to the patient's decision to participate, such as details of study procedures, anticipated benefits, and potential risks of study participation. Sites must inform patients 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 patient is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect patient's legal rights. Financial incentives will not be given to patients. Patients may be compensated for time and travel directly related to the participation in the study. The site shall provide the patient with the Informed Consent form written in a language that is understandable to the patient and that has been approved by the center's EC. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any study-specific procedures. The site will file the signed original in the patient's hospital or research charts, and provide a copy to the patient.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing site's EC according to the EC's reporting requirements.

If, during the study, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.3 Special Circumstances for Informed Consent

This study excludes individuals unable to make the decision to participate in a clinical study on their own or who are unable to fully understand all aspects of the study that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

This study excludes individuals who require emergency use of the device or concomitant interventional procedures, e.g. left atrial appendage closure (LAAC), undertaking during the same procedure.

5.3 **Eligibility Criteria**

5.3.1 Eligibility Assessment

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria to participate in the study. If ANY general exclusion criteria are met, the patient is excluded from the study and cannot be enrolled (recruitment failure).

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

5.3.2 Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria:

1. Subjects is eligible to receive the MitraClip per the current approved MitraClip System IFU. (If any update or amendment on the IFU, the latest version of IFU shall be followed.)
2. Subject is 18 years-old or above.
3. Subjects who give consent for study procedure.

5.3.3 Exclusion Criteria

Subjects must NOT MEET ANY of the following exclusion criteria:

1. Subject cannot tolerate procedural anticoagulation or anti-platelet regimen.
2. Subject with active endocarditis of mitral valve.
3. Subject with rheumatic mitral valve disease.
4. Subject with echocardiographic evidence of intracardiac, IVC or femoral venous thrombus.
5. Subject is unlikely to survive the protocol follow up period of 12-months after device implant.
6. Subject has insufficient or lost ability to maintain their will and rights.
7. Subject is illiterate.
8. Pregnant or nursing subjects and those who plan pregnancy during the study follow-up period
9. Subject participates in another clinical study that may impact the follow-up or results of this study.

5.4 Subject Enrollment and Registration

The subject is considered to be enrolled in the study upon signing and dating the informed consent form. Subjects will be considered registered upon femoral vein puncture for transseptal access in preparation for MitraClip System insertion.

5.5 Subject Withdrawal and Discontinuation

Each registered subject shall remain in the study until completion of the required follow-up period; however, a subject's participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. If the subject decides to withdraw prior to the 1-year follow-up visit, all available data prior to formal documentation of withdrawal from the study must be collected. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Investigator judgment of subject discontinuation
- Subject lost-to-follow-up as described below

Sites must notify the Sponsor of the reason(s) for subject discontinuation. Investigators must also report this to their respective EC as defined by their institution's procedure(s).

No additional follow-up is required or data recorded from subjects once withdrawn from the study, except for the status (deceased/alive).

However, if a subject withdraws from the study due to problems related to the safety or performance of the device under study, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the study.

In case of subject voluntary withdrawal, the site should make attempts to schedule the subject for a final study visit.

Lost-to-Follow-up:

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, the site should send a letter (certified if applicable) to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-study cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

5.6 Number of Subjects

The study will register a minimum of 50 subjects and maximum of approximately 100 subjects.

5.7 Total Expected Duration of the Clinical Study

[redacted]

[redacted]

6 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline

6.1.1 Transthoracic & Transesophageal Echocardiograms to Confirm Subject Eligibility

Eligibility assessments based on transthoracic echocardiogram (TTE) must be performed based on images obtained within 90 days prior to MitraClip procedure. Eligibility assessments based on transesophageal echocardiogram (TEE) must be performed based on images obtained within 180 days prior to procedure.

The TTE and TEE images obtained by sites are submitted to the ECL for analysis.

6.1.2 Clinical Assessments

Within 14 days prior to the MitraClip procedure, a baseline visit must be completed. A complete list of clinical assessments to be completed at the baseline is listed in **Table 1 presents the Clinical** Evaluation Schedule detailing assessments at each visit. These clinical assessments are standard assessments for most cardiac/structural heart interventional procedures and therefore should be administered per standard of care at each Institution.
Table 1: Clinical Evaluation Schedule. Clinical assessments at baseline include heart rate, blood pressure, Kansas City Cardiomyopathy Questionnaire (KCCQ), New York Heart Association (NYHA) Functional Class, Six Minute Walk Test (6MWT) distance, blood test, STS Mortality Risk Score (for mitral valve replacement), and EuroScore II assessments. Concomitant cardiac medications will also be collected at this visit.

6.1.3 12-Lead ECG

A 12-lead ECG must be performed within 24 hours prior to the MitraClip procedure to rule out an acute ischemia or myocardial infarction (**Table 1 presents the Clinical** Evaluation Schedule detailing assessments at each visit. These clinical assessments are standard assessments for most cardiac/structural heart interventional procedures and therefore should be administered per standard of care at each Institution.
Table 1: Clinical Evaluation Schedule).

6.2 Anticoagulation and Antiplatelet

Discontinue the use of warfarin for at least three (3) days prior to the scheduled MitraClip procedure and ensure that the international normalized ratio (INR) ≤ 1.7. Similarly, discontinue dabigatran or factor Xa inhibitors for a sufficient duration to ensure restoration of normal coagulation. Subjects may be treated with heparin during this period at the

[redacted]

treating physician's discretion. If heparin is used, it must be discontinued ≥ 4 hours prior to the MitraClip procedure for intravenous unfractionated heparin (UFH).

Administer a dose of clopidogrel or other thienopyridines, at a dosage determined by the Investigator, either just prior to, or immediately following the procedure. If aspirin is to be used, a dose of 325 mg may be administered either just prior to, or immediately post-MitraClip procedure.

6.3 Subject Preparation

Prior to the MitraClip procedure, subjects must be assessed to ensure there is no significant change in the subject's overall condition (e.g., stroke, MI, active infection, endocarditis, hemodynamic instability, etc.) that would preclude treatment. If the subject has experienced any significant change that would preclude treatment, the subject must be treated and reassessed for the study. Such subjects are not considered registered.

Prior to the MitraClip procedure, baseline activated clotting time (ACT) must be determined following transseptal puncture for the MitraClip procedure. ACT and heparin administration (or alternative anticoagulation therapy) must be recorded.

Subjects must be prepared for the procedure as per the institution's standard practice for a percutaneous procedure, general anesthesia, and TEE.

6.4 MitraClip Procedure

Refer to IFU including storage and handling requirements, preparation for use, pre-use checks of safety and performance, and precautions to be taken after use.

Subjects are required to undergo an additional transesophageal (TEE) echocardiogram immediately preceding initiation of the MitraClip procedure to rule out the presence of intracardiac mass, thrombus or vegetation. This echocardiogram will not be submitted to the Echocardiography Core Laboratory.

If a thrombus is identified, the subject may be pharmacologically treated to resolve the thrombus and, if successful, the subject may be reassessed for the MitraClip China PMS Study.

Femoral vein transseptal catheterization will be completed in accordance with the IFU. Subjects will be considered registered upon femoral vein puncture for transseptal access in preparation for the MitraClip System insertion. Following transseptal crossing, administer intravenous heparin (or alternative anticoagulation therapy; e.g., bivalirudin) in accordance with standard hospital practice. Maintain an ACT (activated clotting time) of > 250 seconds throughout the procedure.

The Steerable Guide Catheter (Guide) is inserted into the femoral vein and advanced across the transseptal puncture. Fluoroscopic and echocardiographic guidance will be used during the procedure to visualize the devices and the vasculature and cardiac

anatomy. For subjects with renal dysfunction, intravenous contrast should not be used during the procedure unless absolutely necessary.

The Guide is positioned over the mitral valve and the MitraClip Delivery System is inserted into the Guide and properly positioned over the mitral valve. The MitraClip Delivery Catheter is advanced until the MitraClip device emerges from the tip of the Guide into the left atrium. Manipulations of the catheter tip (via the control knobs on the handles) will continue in the left atrium until the MitraClip device is properly oriented perpendicular to the line of coaptation of the mitral valve. The MitraClip device is opened and advanced across the mitral valve into the ventricle then pulled back to grasp the leaflets. Two-dimensional and/or 3-dimensional echocardiography and color flow Doppler are used to evaluate the presence of a double orifice, leaflet insertion, MitraClip device position and residual MR. If the MitraClip device is not positioned properly or MR has not been adequately reduced, additional grasping may be attempted and the MitraClip device may be inverted in the left atrium as required for additional grasping attempts. When placement is successful, the MitraClip device is closed and deployed from the Delivery Catheter. The catheters are then removed from the subject.

If MR reduction is not adequate, an additional MitraClip device may be placed at the implanter's discretion, depending on patient clinical condition, mitral valve area and mean Mitral Valve Gradient.

6.5 Post–MitraClip Procedure

Immediately following the MitraClip procedure, heparin (or alternative anticoagulation therapy; e.g., bivalirudin) must be discontinued and the ACT should be monitored in accordance with hospital standard of care. Vascular sheaths should be removed according to usual hospital practice.

Administer additional intravenous doses of antibiotics at approximately 6 and 12 hours (or per institutional guidelines) after the completion of the procedure.

Subjects will receive standard post-cardiac catheterization procedure care as judged appropriate by the Investigator.

Subject weight, blood pressure, heart rate and temperature must be obtained prior to subject discharge from the hospital.

At discharge, each subject implanted with MitraClip device must be provided an Implant Identification Card. An Implant Identification Card is included in the package with each MitraClip System. The subject must be instructed to keep this Implant Identification Card with them at all times. The serial number of all implanted MitraClip device(s) must be recorded on the Implant Identification Card.

The Investigator must instruct all subjects who receive the MitraClip device of the need for prophylaxis for endocarditis, as recommended in the guidelines for the prevention and treatment of infective endocarditis (JSC 2008)[5]. Subjects must be instructed to notify the

Investigator or the subject's primary care physician in the event that a procedure recommended by this Guideline is planned, so that prophylactic antibiotics can be prescribed.

Post-MitraClip procedure anticoagulation is recommended per the Investigator's discretion as follows:

1. Reinitiate warfarin, dabigatran or factor Xa inhibitor (if discontinued for the MitraClip procedure) at pre-procedure levels or as appropriate. If chronic oral anticoagulation is used, then aspirin and ticlopidine use are not recommended, but are allowed if otherwise indicated for other conditions.

2. If chronic oral anticoagulation is not used, it is strongly recommended that either daily clopidogrel or other thienopyridines, at a dosage determined by the Investigator and/or aspirin (100 mg) is administered for 6 months or longer.

6.6 Follow-up for All Subjects

Clinical follow-up will be performed at the following intervals for all registered subjects:

- Discharge post-MitraClip procedure
- 30 days follow-up office visit (+14 days) (this visit must be conducted even if subject is in hospital)
- 1 year follow-up office visit (365 ± 45 days)

During the follow-ups, all subjects will be treated per applicable standards of care consistent with the subject's condition. Subjects implanted with the MitraClip device must also be evaluated for device integrity. If MitraClip was not implanted, the subject will be followed for 30 days for safety monitoring.

Table 1 presents the Clinical Evaluation Schedule detailing assessments at each visit. These clinical assessments are standard assessments for most cardiac/structural heart interventional procedures and therefore should be administered per standard of care at each Institution.

Table 1: Clinical Evaluation Schedule

Assessments	Screening	Baseline	Hospital Discharge	30 Days	1 Year
				+14 days	± 45 days
Medical history	X	X[1]			
Evaluation by Local Site Heart Team	X				
Weight, temperature, blood pressure and heart rate	X	X[2]	X	X	X
Concomitant cardiac medications including dose		X[1]	X	X	X
CBC with differentials and platelet count		X[1]	X	X	X
Serum Creatinine		X[1]	X	X	X
Blood Urea		X[1]	X	X	X
BNP and NT-proBNP		X[1]	X	X	X
CK and CK-MB		X[1]	X	X	X
Pregnancy test		X[1,3]			
STS Mortality Risk Score for mitral valve replacement		X[1]			
EuroScore II		X[1]			
12-Lead ECG		X[2]			
Transesophageal Echocardiography (TEE)	X[4]	X[5]			
Transthoracic Echocardiography (TTE)	X[6]	X[7]	X	X	X
NYHA Classification		X[1]		X	X
Six Minute Walk Test (6MWT) distance		X[1]		X	X
KCCQ		X[1]		X	X
Adverse events			X	X	X

1. Within 14 days prior to MitraClip procedure
2. Performed within 24 hours prior to MitraClip procedure
3. Female subject within the child bearing age only
4. Within 180 days prior to MitraClip procedure;
5. TEE immediately prior to the MitraClip procedure
6. Within 90 days prior to MitraClip procedure

7. Screening test can be used if the screening test is within 14 days prior to MitraClip procedure

6.7 Additional Follow-up Visits for All Subjects

Additional subject visits may occur as clinically warranted. The following information must be collected as applicable:

- Adverse events
- Concomitant cardiovascular medications including dosage
- Hospitalizations
- Mitral valve surgery
- Additional MitraClip procedure(s)

7 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical study adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient hospitalization or prolongation of existing hospitalization, or
4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or

[redacted]

5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

7.1.3 Device Deficiency/Device malfunction

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or CIP.

7.2 **Device Relationship**

Determination of whether there is a reasonable possibility that a product or device caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate source documents and eCRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.3 **Adverse Event and Device Deficiency/Device Malfunction Reporting**

7.3.1 Adverse Event Reporting

All adverse events will be collected on each subject through the femoral vein puncture for transseptal access in preparation for MitraClip System insertion to the 1-year follow-up visit. Adverse events will not be collected for screen failure subjects.

The event course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Unchanged, chronic conditions and elective procedures (e.g., routine dental procedures) for a pre-existing condition are not considered AEs and should not be recorded on the adverse event page of the eCRF.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1) the investigator determined that the value is clinically significant,
2) the abnormal lab value required intervention, or
3) the abnormal lab value required subject termination from the study.

Serious Adverse Event Reporting:

Serious adverse events, as outlined above, should be reported to the Sponsor, EC, and local Food and Drug Administration agency as soon as possible but no later than 24 hours from the site becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware of the SAE must be recorded in the source document. The Investigator will further report the event to the local GCP office and the Ethics Committee (EC) according to the institution's reporting requirements.

Serious adverse events, as outlined above, should be reported on the SAE Notification Form in the occurrence that the EDC System is not available. This does not replace the EDC reporting system. All information must still be entered in the EDC system once the system is back to normal function.

Study site	Reporting timelines
All Sites	Sites should report SAEs to regulatory authorities and the Sponsor no later than 24 hours from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must record the date the site staff became aware that the event met the criteria of an SAE in the source document. The Investigator will further report the SAE to the local EC according to the institution's EC reporting requirements.

[redacted]

If more detailed information is obtained after the initial reporting, additional report shall be prepared and submitted as follow up and/or closing reporting.

7.3.2 Device Deficiency/Device Malfunction Reporting

All device deficiencies/malfunctions should be reported within the EDC System on the appropriate eCRF form. The investigator should report all device deficiencies /malfunctions to the Sponsor as soon as possible but no later than outlined below.

Study site	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 2 business days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must report device deficiencies/malfunctions to the EC per the site's local requirements.

Sites should return the deficiency/malfunction device, if not implanted or not remaining in the subject, to the Sponsor.

7.3.3 Adverse Event Reporting to Regulatory Authorities by the Sponsor

The Sponsor will report the SAEs and reportable device deficiencies/malfunctions to the regulatory authority, per local requirements. The Sponsor will also notify all the other study sites conducting the study and ECs of the occurrence of the SAEs.

8 STATISTICAL CONSIDERATIONS

This is a post market study of consecutive consented, eligible subjects who have attempted treatment of the MitraClip System at participating sites. No pre-specified hypothesis tests are planned for the MitraClip China PMS. The following section describes the statistical methods for the MitraClip China PMS.

8.1 Analysis Populations

8.1.1 Attempted Procedure Population (AP)

[redacted]

8.1.2 Implanted Population (IP)

[redacted]

8.2 Statistical Analyses

Descriptive analysis will be performed to summarize baseline, APS, clinical and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in this section below will be used.

For continuous variables such as age, means, standard deviations, and 95% confidence intervals for the mean will be calculated. [redacted]

[redacted]

8.2.1 Primary Endpoints Analyses

The study has two primary endpoints: freedom from MAE at 30 days and APS, both defined in **Section 4.1**.

[redacted]

8.3 Sample Size Calculations and Assumptions

A minimum of 50 subjects and a maximum approximately 100 subjects will be registered at up to 10 sites. [redacted]

8.4 Time of Analysis

The primary endpoint analyses will be performed when all registered subjects complete their 30-day follow-up.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/site will permit direct access to source data/documents for study-related monitoring, audits, EC review, and regulatory inspections.

Subjects providing informed consent agree to allow Sponsor or designee access and copying rights to pertinent information in their medical records concerning their participation in this study. The Investigator will obtain, as part of the informed consent, permission for study monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the evaluation of the study device. Sites will be selected based upon review of a recent site assessment and the qualifications of the Principal Investigator at the site. Investigators will be selected after submission of recent curriculum vitae and confirmed 1) has sufficient clinical experience and training for conducting the study, 2) has enough time to conduct the study. The Principal Investigator will assign sub-investigators and study collaborators. All Investigators and study collaborators must be trained on the protocol and study procedures prior to enrolling subjects.

[redacted]

In this study, all MitraClip implanters will be designated in advance upon consultation with the Principal Investigator of each site. All MitraClip implanters must have undergone the MitraClip Therapy Training program provided by the Sponsor.

10.2 Study Finance and Agreements

Abbott will finance this PMS and will compensate study sites for participation in the study per the conditions of agreement between Abbott and the study site.

10.3 Protocol Amendments

The Sponsor will provide approved protocol amendments to the Investigators prior to implementing the amendment. The Principal Investigator is responsible for notifying the EC or equivalent committee of the protocol amendment (administrative changes) or obtaining EC's approval of the protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the protocol amendment.

Sites must document in writing acknowledgement/approval of the protocol amendment by the EC prior to implementation of the protocol amendment. Sites must also provide copies of this documentation to the Sponsor.

10.4 Training

10.4.1 Site Training

All Investigators/study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Training of Investigators/study personnel will include, but is not limited to, device training, the protocol requirements, device usage, electronic case report form completion, study personnel responsibilities, and regulatory requirements.

All Investigators/study personnel that are trained must sign a training log upon completion of the training. Prior to signing the training log, Investigator/study personnel must not perform any study-related activities that are not considered standard of care at the site. Prior to the initiation of the study, the study monitor or designee will visit each site where the study will be conducted. The study monitor

will ensure that sites' study personnel are informed about and understand the study requirements. [redacted]

[redacted]	[redacted]							
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[redacted]								
[redacted]								

[redacted]

[redacted]

[redacted]	[redacted]		
[redacted]			
[redacted]			
[redacted]			

[redacted]

10.5 **Monitoring**

Sponsor and/or designee will monitor the MitraClip China PMS over its duration according to the protocol-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the study according to the protocol and applicable regulations and has signed the Clinical Study Agreement
- The Investigator and his/her staff should have sufficient time and facilities to conduct the study and should have access to an adequate number of appropriate subjects to conduct the study.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.

[redacted]

- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of study-related documents.

10.6 Deviations from Protocol

The Investigator should not deviate from the protocol for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety, and well-being of the subject, or to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

The Sponsor will not grant any waivers for protocol deviations. Sites must report all deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of protocol for evaluation of investigator compliance to the protocol and regulatory requirements and handle according to written procedures. Investigators will inform their EC or equivalent committee of all protocol deviations in accordance with their specific EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or Sponsor's representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the protocol, or any other conditions of the study may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the investigator's participation in the clinical study.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical study records, including source documentation, for inspection during a Quality Assurance audit.

If an investigator is contacted by a Regulatory Agency in relation to this PMS, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study. The Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Sponsor Auditing

The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties and conduct audits in accordance with the audit plan and the operating procedures.

Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.

The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

10.9 Primary Investigator Responsibilities

The responsibilities of the Primary Investigator shall be as follows coordinating among all clinical sites during the clinical trial, organizing investigator meetings at the earlier stage, middle stage and later stage of the trial, and implementing the entire trial together with the sponsor in China and complete the summary report in coordination with the investigators of all the participating investigating sites.

11 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the study.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the end of the study, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change will be provided to the study sites, if requested.

For the duration of the study, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, study progress records, laboratory reports, CRFs, signed ICFs, correspondence with the EC and study monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the study.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this study.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the study sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the study, such as the patient's medical condition, treatment, dates of treatment, etc., into Sponsor's data management systems. The Sponsor discloses as part of the study informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. All parties will observe confidentiality of Personal Information always throughout the study. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Study data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the study. The Sponsor will track and document control all revisions.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. To comply with these regulatory requirements/GCP, sites should include the following information in the subject record at a minimum and if applicable to the clinical study:

- Medical history/physical condition of the subject before involvement in the study sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the clinical study referencing the Sponsor, protocol number, subject ID number, and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- AEs reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.

- Protocol-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding protocol-required and prescription medications taken during the study (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the study
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. This serves as source documentation.

11.4 Electronic Case Report Form Completion

Site research personnel trained on the protocol and CRF completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

eCRF data will be collected for all subjects who are registered into the study.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. The Sponsor will use an electronic audit trail to track any subsequent changes of the entered data.

The following data elements will be collected on eCRFs:

Visit	Data Elements to be Collected
Screening	- Document medical history - Weight, temperature, blood pressure and heart rate - MR severity, MVA and etiology (Functional or Degenerative) based on TTE/TEE - Left ventricular ejection fraction and left ventricular end-systolic dimension based on TTE - Mitral valve anatomy for MitraClip suitability
Baseline (within 14 days prior to subject registration)	- Document medical history - Weight, temperature, blood pressure and heart rate - STS Mortality Risk Score for mitral valve replacement - EuroScore II - MR severity, MVA and etiology (Functional or Degenerative) based on TTE/TEE (screening TTE/TEE can be used if within 14 days) - KCCQ - NYHA Classification

Visit	Data Elements to be Collected
	- Pregnancy test for females of childbearing potential - Blood test (CBC with differentials and platelet count, serum creatinine, urea, CK and CK-MB, BNP and NT-proBNP) - Cardiac medications
Pre-Procedure (within 24 hours prior to subject registration)	- 12-Lead ECG - Weight, temperature, blood pressure and heart rate - ACT and administration of anticoagulation therapy
Procedure	- ACT and administration of anticoagulation therapy - Model and serial number of devices used (whether or not implanted) - Number of devices implanted (if implant unsuccessful, reason for unsuccessful implant) - Procedure and Device times - Length of stay in ICU/CCU/PACU post-procedure
Discharge	- MR severity based on TTE - Weight, temperature, blood pressure and heart rate - Blood test (CBC with differentials and platelet count, serum creatinine, urea, CK and CK-MB, BNP and NT-proBNP) - Cardiac medications
Follow-up (30 days and 1 year)	- MR severity based on TTE - KCCQ - NYHA Classification - Six Minute Walk Test Distance (excluding 30 days) - Weight, temperature, blood pressure and heart rate - Blood test (CBC with differentials and platelet count, serum creatinine, urea, CK and CK-MB, BNP and NT-pro-BNP) - Cardiac medications
Throughout follow-up	Adverse events, device complications or malfunctions, hospitalizations, additional MitraClip procedures, mitral valve surgery, and protocol deviations will be reported as they occur

11.5 **Record Retention**

The Investigator/Site will archive and retain all documents pertaining to the study until 10 years after the completion of the study as per the applicable regulatory record retention requirements. The Investigator/Site must obtain permission from Sponsor in writing before destroying or transferring control of any study records. The Sponsor shall keep the study data until the medical device are withdrawn.

12 ETHICAL CONSIDERATION

12.1 Ethics Committee Review and Approval

The Principal Investigator at each study site will obtain EC approval for the protocol and ICF/other written information provided to the patient prior to consenting and registering patients in this clinical study. The site must receive the approval letter prior to the start of this clinical study and provide a copy to the Sponsor.

Sites will submit any amendments to the protocol as well as associated ICF changes to the EC and written approval obtained prior to implementation, according to each institution's EC requirements.

No changes will be made to the protocol or ICF or other written information provided to the patient without appropriate approvals, including EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical study is completed, the Investigator will advise his/her EC of the progress of this study, per EC requirements. Written approval must be obtained from the EC yearly to continue the study, or according to each institution's EC requirements.

Sites will not perform any investigative procedures, other than those defined in this protocol, on the registered subjects without the written agreement of the EC and the Sponsor.

13 CLINICAL STUDY CONCLUSION

The clinical study will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of study closure.

14 PUBLICATION POLICY

[redacted]

[redacted]

[redacted]

15 RISK ANALYSIS

Patients with symptomatic MR who are difficult for mitral valve surgery have limited therapeutic options. Patients judged difficult for surgery with untreated moderate-to-severe or severe MR present with a high rate of heart failure hospitalizations, poor quality of life, and impaired functional capacity.

In the context of accumulated evidence worldwide, the MitraClip China PMS serves as a bridge to previous clinical data. Based on the available data, it is likely that the benefits significantly outweigh any potential risks to symptomatic MR patients in China.

15.1 Anticipated Clinical Benefits

[redacted]

[redacted]

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Per the MitraClip System IFU, the anticipated events on **Table 15-1** have been identified as possible.

Table 15-1: Potential Complications and Adverse Events (MitraClip System IFU)

Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex)	Hemorrhage requiring transfusion
Aneurysm or pseudo-aneurysm	Hypotension / hypertension
Arrhythmias	Infection
Atrial fibrillation	Lymphatic complications
Atrial septal defect requiring intervention	Mesenteric ischemia
Arterio-venous fistula	Mitral stenosis
Bleeding	Mitral valve injury
Cardiac arrest	MitraClip Implant erosion, migration or malposition
Cardiac perforation	MitraClip Implant thrombosis
Cardiac tamponade / Pericardial Effusion	MitraClip System component(s) embolization
Chordal entanglement/rupture	Multi-system organ failure
Coagulopathy	Myocardial infarction
Conversion to standard valve surgery	Nausea/vomiting
Death	Pain
Deep venous thrombus (DVT)	Peripheral ischemia
Dislodgement of previously implanted devices	Prolonged angina
Dizziness	Prolonged ventilation
Drug reaction to anti-platelet / anticoagulation agents / contrast media	Pulmonary congestion
Dyskinesia	Pulmonary thrombo-embolism
Dyspnea	Renal insufficiency or failure
Edema	Respiratory failure / atelectasis / pneumonia
Emboli (air, thrombus, MitraClip Implant)	Septicemia
Emergency cardiac surgery	Shock, Anaphylactic or Cardiogenic
Endocarditis	Single leaflet device attachment (SLDA)
Esophageal irritation	Skin injury or tissue changes due to exposure to ionizing radiation
Esophageal perforation or stricture	Stroke or transient ischemic attack (TIA)
Failure to deliver MitraClip to the intended site	Urinary tract infection
Failure to retrieve MitraClip System components	Vascular trauma, dissection or occlusion
Fever or hyperthermia	Vessel spasm
Gastrointestinal bleeding or infarct	Vessel perforation or laceration
Hematoma	Worsening heart failure
Hemolysis	Worsening mitral regurgitation
	Wound dehiscence

15.3 Residual Risk Associated with MitraClip System

This is a PMS on an NMPA approved commercially available device. There is no investigational device being used as part of this study.

[redacted]

15.4 Risk Associated with Participation in This Study

[redacted]

15.5 Possible interaction with Protocol-Required Concomitant Medications

This is a post-market study being conducted under standard of care medications. There are no protocol-required medications being used as part of this study.

15.6 Steps Taken to Control or Mitigate Risks

Per the MitraClip System IFU, “Use of the MitraClip Delivery System should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and to those physicians trained in the proper use of the system”.

Risks associated with the use of the device during this clinical study are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements.

The contraindications, warnings and precautions are listed in the MitraClip System IFU that will be provided with all devices to be used during this study.

15.7 Risk to Benefit Rationale

Patients with symptomatic MR have limited therapeutic options. Patients judged difficult for surgery with untreated moderate-to-severe or severe MR present with a high rate of heart failure hospitalizations, poor quality of life, and impaired functional capacity.

[redacted]

The MitraClip System provides patients with a minimally invasive, safe option to reduce MR that affords short recovery times with amelioration of symptoms, and a resulting improvement in both cardiac function and quality of life.

The risk-benefit profile of the MitraClip System has been established in patients with moderate to severe and severe DMR or FMR, who may be high surgical risk candidate per the EVEREST family and COAPT trials, and has been further demonstrated through the European commercial experience, including ACCESS-EU and national registries such as TRAMI, GRASP and EXPAND. In total, over 100,000 patients have been treated with the MitraClip system worldwide.

All protocol required clinical assessments are standard assessments for most cardiac/structural heart interventional procedures, and will be administered per standard of care at each Institution. As such these assessments do not involve additional risks to the trial participants. Per protocol required concomitant anticoagulation and antiplatelet medications should be administered as described in the drug summary of product characteristics.

Subjects participating in the study have a small risk of loss of confidentiality as part of the data collection process. This risk is mitigated to as low as possible with the use of data collection systems, methods and procedures that are used commonly in clinical research. This includes the use of only validated electronic systems, the training of study personnel and the use of de-identified data for all data entry. Based upon the established safety profile of the MitraClip implant; the low risk of loss of confidentiality is adequately mitigated to justify use of the MitraClip implant to treat patients for this study.

16 APPENDICES

16.1 Appendix I: Abbreviations and Acronyms

Acronym or Abbreviations	Complete Phrase or Definition
ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial Fibrillation
APS	Acute Procedural Success
ASA	Acetylsalicylic Acid
ASD	Atrial Septal Defect
BNP and NT-proBNP	Brain Natriuretic Peptide and N-Terminal Pro-B Type Natriuretic Peptide
CBC	Complete Blood Count
CCU	Critical Care Unit
CDS	Clip Delivery System
CE	Conformité Européenne (EU)
CIP	Clinical Investigational Plan
CK-MB	Creatinine Kinase-MB
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardioverter Defibrillator
CT	Cardiothoracic
DD	Device Deficiency
DDCD	Duke Databank of Cardiovascular Disease
DM	Device Malfunction
DMR	Degenerative Mitral Regurgitation
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECL	Echocardiography Core Laboratory
eCRF	Electronic CRF
EDC	Electronic Data Capture
EF	Ejection Fraction
FMR	Functional Mitral Regurgitation
HRR	High Risk Registry
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IFU	Instructions for Use

LBBB	Left Bundle Branch Block
LV	Left Ventricle or Left Ventricular
LVEDD	Left Ventricular End Diastolic Dimension
LVEDV	Left Ventricular End Diastolic Volume
LVESD	Left Ventricular End Systolic Dimension
LVESV	Left Ventricular End Systolic Volume
LVEF	Left Ventricular Ejection Fraction
MAE	Major Adverse Events
MI	Myocardial Infarction
MLWHF	Minnesota Living with Heart Failure
MOPs	Manual of Operations
MR	Mitral Regurgitation
NYHA	New York Heart Association
PACU	Post-Anesthesia Care Unit
PE	Product Experience
PMS	Post Market Study
QoL	Quality of Life
RCT	Randomized Clinical Trial
SLDA	Single Leaflet Device Attachment
STS	Society of Thoracic Surgeons
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal Echocardiogram
TTE	Transthoracic Echocardiogram
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
VARC	Valve Academic Research Consortium

16.2 Appendix II: Definitions

The following definitions will be used in the MitraClip China protocol.

ADVERSE EVENT
An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects (including events related to the procedures involved), users or other persons, whether or not related to the medical device. For users or other persons, this definition is restricted to events related to medical devices.

ANTICIPATED ADVERSE EVENT
Abbott Clinical definition (derived from ISO14155, MEDDEV 2.7.3): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report, as documented in the IFU or study protocol.

ATRIAL FIBRILLATION (AF)

Heart Rhythm Society Guidelines

Paroxysmal: Recurrent (≥ 2) atrial fibrillation episodes that terminate spontaneously within 7 days.

Persistent: Atrial fibrillation that is sustained beyond 7 days or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion.

Longstanding Persistent AF: Continuous atrial fibrillation of greater than 1-year duration.

Permanent: Atrial fibrillation in which cardioversion has failed or not been attempted.

ATRIAL SEPTAL DEFECT
Defect ('hole') in the septum between the left and right atria; considered clinically significant if it requires percutaneous or surgical intervention (repair of ASD completed at the time of surgery for other reasons, but not as the primary reason for surgery, is not counted as ASD.)

CHRONIC MITRAL REGURGITATION
Mitral regurgitation persisting for a long time or constantly recurring; having a slow progressive course of indefinite duration (e.g., non-acute)

DEATH
Defined as all causes of death for the primary safety Major Adverse Event (MAE) Endpoint. Death is further divided into 2 categories

1. CARDIOVASCULAR DEATH (VARC)
Cardiovascular death is defined by the Valve Academic Research Consortium (VARC)[5] as any one of the following:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

2. NON-CARDIOVASCULAR DEATH
Any death not covered by the definitions for Cardiovascular Death, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

DEVICE EMBOLIZATION
Detachment of the deployed MitraClip device from both mitral leaflets

DEVICE THROMBOSIS
Evidence of the formation of an independently moving thrombus on any part of the MitraClip device evidenced by echocardiography or fluoroscopy. If the MitraClip device is explanted or an autopsy is performed, this diagnosis should be confirmed.

ENDOCARDITIS
Defined as a diagnosis of endocarditis based on the following Duke criteria.

Duke Criteria
(From The ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease, JACC, Vol 32, No.5, November 1, 1998:pg1541, Table 21)

[redacted]

Pathological Criteria

Microorganisms: culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, or

Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

OR

Clinical Criteria

Major Criteria

Persistently positive blood cultures:

Typical organisms for endocarditis: *Streptococcus viridans, S bovis*, "HACEK" group, community acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus

Persistent bacteremia:

≥ 2 positive cultures separated by ≥12 hours or ≥ 3 positive cultures ≥ 1 h apart or 70% blood culture samples positive if ≥ 4 are drawn

Evidence of endocardial involvement

Positive echocardiogram

Oscillating vegetation

Abscesses

Valve perforation

New partial dehiscence of prosthetic valve

New valvular regurgitation

Minor Criteria

Predisposing heart condition:

MVP, bicuspid aortic valve, rheumatic or congenital heart disease, intravenous drug use

Fever

Vascular phenomena:

Major arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, Janeway lesions

Immunologic phenomena

Glomerulonephritis, Osler's nodes, Roth spots , and rheumatoid factor

Positive blood culture: not meeting major criteria

Echocardiogram: positive but not meeting major criteria

Diagnosis

[redacted]

2 major criteria or 1 major plus 3 minor criteria or 5 minor criteria

ETIOLOGY OF MITRAL REGURGITATION
Etiology of mitral regurgitation will be determined as either Degenerative or Functional:

1. **DEGENERATIVE MITRAL REGURGITATION**
   Mitral regurgitation primarily due to abnormality of the mitral apparatus

2. **FUNCTIONAL MITRAL REGURGITATION**
   Global or regional left ventricular wall motion abnormalities causing leaflet restriction or tethering with or without dilatation of the mitral annulus, but with no significant abnormalities of the mitral leaflet

GASTROINTESTINAL COMPLICATIONS
Complications as a result of the MitraClip procedure affecting the gastrointestinal tract requiring surgery. May include fecal impaction, bowel obstruction, etc.

HOSPITALIZATION (ALL-CAUSE)
Defined as admission to inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay. Excludes hospitalizations planned for pre-existing conditions unless there is worsening in the baseline condition.

HEART FAILURE HOSPITALIZATION
Defined as an event that meets the following criteria:

A. Requires hospitalization with treatment in any inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay,

AND

B. Subject has clinical signs and/or symptoms of heart failure, including new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue, worsening functional capacity or activity intolerance, or signs and/or symptoms of volume overload,

AND

C. Results in intravenous (e.g., diuretic or vasoactive therapy) or invasive (e.g., ultrafiltration, IABP, mechanical assistance) treatment for heart failure.

For the purpose of the protocol, overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, do not meet the protocol definition of hospitalization.

OTHER CARDIOVASCULAR HOSPITALIZATION
Defined as treatment in any inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay for conditions such as coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis and peripheral vascular disease, not related to heart failure as defined.

NON-CARDIOVASCULAR HOSPITALIZATION
Hospitalizations that are not heart failure or other cardiovascular hospitalizations, as defined above, will be categorized as non-cardiovascular hospitalizations.

MAJOR BLEEDING
Major bleeding is defined as bleeding ≥ Type 3 based on a modified Bleeding Academic Research Consortium (BARC)[6] definition:

- Type 3
  - Type 3a
    - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
    - Any transfusion with overt bleeding
  - Type 3b
    - Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
    - Bleeding requiring intravenous vasoactive agents
  - Type 3c
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
    - Subcategories confirmed by autopsy or imaging or lumbar puncture
    - Intraocular bleed compromising vision
- Type 4: CV Surgery-related bleeding
  - Perioperative intracranial bleeding within 48 h
  - Reoperation after closure of sternotomy for the purpose of controlling bleeding

- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

- Type 5: Fatal bleeding
  - Type 5a
    - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
  - Type 5b
    - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin)
†Cell saver products are not counted

MAJOR VASCULAR COMPLICATION
Any major complication, relating to, or affecting, the circulatory system as a result of the MitraClip procedure, including new onset of any of the following:

- Hematoma at access site >6 cm.;
- Retroperitoneal hematoma;
- Arterio-venous fistula;
- Symptomatic peripheral ischemia/ nerve injury with clinical signs or symptoms lasting >24 hours;
- Vascular surgical repair at catheter access sites;
- Pulmonary embolism;
- Ipsilateral deep vein thrombus; or
- Access site-related infection requiring intravenous antibiotics and/or extended hospitalization.

MITRAL VALVE STENOSIS
Defined as a mitral valve orifice of less than 1.5 cm^2 as measured by the Echocardiography Core Laboratory.

MYOCARDIAL INFARCTION
Myocardial infarction (MI) classification and criteria for diagnosis is defined as follows:

Peri-procedural MI (≤ 72 hours after MitraClip procedure)
Mandatory: CK-MB (preferred) ≥10x ULN within 72 hrs. post-MitraClip procedure in patient with normal baseline CK-MB

OR

[redacted]

Mandatory: CK-MB ≥5x ULN within 72 hrs. post-MitraClip procedure in patient with normal baseline CK-MB *plus* new pathological Q-waves in ≥2 contiguous leads, or new LBBB

Post-surgery
Mandatory: CK-MB ≥10x ULN (preferred) within 24 hrs. of cardiothoracic surgery *plus 1 of the following:*

- New pathological Q-waves in ≥2 contiguous leads or new persistent LBBB on ECG ≥30 min. and ≤72 hrs. post-CABG cardiothoracic surgery, or
- New substantial wall motion abnormalities by imaging except new septal or apical abnormalities.

Spontaneous MI (>72 hours after MitraClip procedure)
Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (CK-MB) with at least one value above the upper limits of normal (ULN), together with evidence of myocardial ischemia with at least one of the following:
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
  - New pathological Q waves in at least two contiguous leads
  - Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA CLASS)

Class I	Patients with cardiac disease but without resulting limitations of physical activity.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

[redacted]

Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NON-ELECTIVE (i.e., URGENT or EMERGENT) CARDIOVASCULAR SURGERY FOR PROCEDURE OR DEVICE RELATED EVENTS

Cardiovascular surgical procedure performed for device related complication requiring surgery within 24 hours of onset of adverse event. If non-urgent surgery was performed within 24 hours of the onset of the adverse event but was not required within this timeframe, it will not be considered "non-elective". Examples of Device Related Complications are myocardial perforation, Single Leaflet Device Attachment, embolization of the MitraClip device or MitraClip System components, iatrogenic atrial septal defect, or the need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device.

SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is defined as an event:

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
5. in-patient hospitalization or prolongation of existing hospitalization, or
6. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

SINGLE LEAFLET DEVICE ATTACHMENT (SLDA)
Defined as unilateral MitraClip detachment from one leaflet, as assessed by the Echocardiography Core Laboratory or during mitral valve surgery. Reasons for MitraClip Detachment include leaflet tearing, MitraClip unlocking, MitraClip fracture or inadequate MitraClip placement. Not included are any fractures or other failures of the MitraClip that do not result in MitraClip detachment from one or both leaflets.

STROKE and TIA
Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Stroke may be classified as ischemic or hemorrhagic with appropriate sub-definitions. Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.

An entity closely related to ischemic stroke is transient ischemic attack (TIA). TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction. The difference between TIA and ischemic stroke is the presence of infarction. In the absence of affirmative evidence confirming the presence or absence of infarction, a symptom duration of 24 hours will be used to distinguish TIA from ischemic stroke. By definition, TIA does not produce lasting disability.

Although imaging (typically, MRI for acute and chronic ischemia and hemorrhage, and CT for acute and chronic hemorrhage and chronic ischemia) is often used to supplement the clinical diagnosis of stroke, a diagnosis of stroke may be made on clinical grounds alone.

Diagnostic criteria
Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or

aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke Stroke – Duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death TIA – Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist* Confirmation of the diagnosis by at least one of the following: – Neurologist or neurosurgical specialist – Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke classification Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic

* Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or Brain MRI).

RENAL FAILURE

New need for dialysis or a creatinine increasing to 3.5 mg/dL or greater
Note: Increase of creatinine less 1.0 mg/dL over baseline is NOT considered renal failure

SYMPTOMATIC MITRAL REGURGITATION
Symptomatic refers to limitation of physical activity (i.e. NYHA Classification II, III or IV)

VULNERABLE POPULATION (ISO14155 Definition)
Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapables of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor**,** members of the armed forces, and persons kept in detention.

16.3 Appendix III: Transthoracic Echocardiography Acquisition Guidelines

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16.4 Appendix IV: Revision History

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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16.5 Appendix V: Protocol Summary

Trial Name and Number	MitraClip China PMS CRD956-PMS
Title	MitraClip China PMS: A Prospective, Multi-Center, Single-Arm, Post Market Study of the MitraClip System for the Treatment of Symptomatic Mitral Regurgitation in China (CRD956-PMS)
Objectives	To confirm the evidence of safety and efficacy of MitraClip system in Chinese subjects with a post market setting.
Devices	MitraClip System (CDS0601-NTR, CDS0601-XTR, SGC0301)
Targeted number of subjects to receive study device	A minimum of 50 subjects and a maximum of approximately 100 subjects at up to 10 sites in China.
Study Design	• Prospective, multi-center, single-arm, post market study • Subjects will be evaluated at baseline, index procedure, discharge, 30 days and 1 year
Primary Endpoints	• Acute Procedural Success (APS) • Freedom from Major Adverse Event (MAE) rate at 30 days
Descriptive Endpoints	Clinical Endpoints: The following descriptive clinical endpoints will be assessed at all scheduled office visits. • All-cause mortality • Freedom from the components of MAE • NYHA Functional Class • Kansas City Cardiomyopathy Questionnaire (KCCQ) Quality of Life (QoL) scores • Six Minute Walk Test (6MWT) distance • Mitral valve surgery (including type of surgery), including reason for intervention • Additional MitraClip System intervention, including reason for intervention • Number of hospitalizations and reason for hospitalization (i.e. heart failure, cardiovascular, non-cardiovascular) in study period • Device-related complications: defined as a composite of single leaflet device attachment (SLDA), device embolization, clinically significant iatrogenic septal defect or mitral stenosis that requires intervention • Major bleeding

	Device and Procedure-Related Endpoints: • Implant Success Rate: Defined as the rate of successful delivery and deployment of one or more MitraClip devices and retrieval of the delivery catheter • Device Procedure Time: Defined as the time elapsed from the start of the transseptal procedure to the time the Steerable Guide Catheter is removed • Total Procedure Time: defined as the time elapsed from the first of any of the following: intravascular catheter placement, anesthesia or sedation, or transesophageal echocardiogram (TEE), to the removal of the last catheter and TEE • Device Time: Defined as the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System (CDS) is retracted into the Steerable Guide Catheter • Fluoroscopy Time: defined as the total minutes of exposure to fluoroscopy during the MitraClip procedure • Length of stay in Intensive Care Unit/Critical Care Unit/Post-Anesthesia Care Unit (ICU/CCU/PACU) • Length of hospital stay for index MitraClip procedure Echocardiographic Endpoints: The following descriptive echocardiographic endpoints will be assessed at all scheduled office visits. • MR Severity Grade • Effective Regurgitant Orifice Area • Regurgitant Volume (RV) • Regurgitant Fraction (RF) • Left Ventricular End Diastolic Volume (LVEDV) • Left Ventricular End Systolic Volume (LVESV) • Left Ventricular End Diastolic Dimension (LVEDD) • Left Ventricular End Systolic Dimension (LVESD) • Left Ventricular Ejection Fraction (LVEF) • Right Ventricular Systolic Pressure (RVSP) • Mitral Valve Area (MVA) • Mean Mitral Valve Pressure Gradient (MVG) • Systolic Anterior Motion of the mitral valve (present or absent) • Forward Stroke Volume (FSV) • Cardiac Output (CO) • Cardiac Index (CI)
Subject Follow-up	Subjects will have scheduled office visit evaluations for assessment of study endpoints at hospital discharge, 30 days and 1 year.

Inclusion Criteria	• Subject is eligible to receive the MitraClip per the current approved MitraClip System IFU • Subject is 18-year-old or above • Subject who gives consent for study procedure
Exclusion Criteria	• Subject cannot tolerate procedural anticoagulation or anti-platelet regimen • Subject with active endocarditis of mitral valve • Subject with rheumatic mitral valve disease • Subject with echocardiographic evidence of intracardiac, IVC or femoral venous thrombus • Subject is unlikely to survive the protocol follow up period of 12-months after device implant • Subject has insufficient or lost ability to maintain their will and rights • Subject is illiterate • Subject participates in another clinical study that may impact the follow-up or results of this study

16.6 **Appendix VI: References**

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