



CLINICAL INVESTIGATIONAL PLAN 11-512

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (The COAPT Trial)

A Clinical Evaluation of the Safety and Effectiveness of the MitraClip® System for the Treatment of Functional Mitral Regurgitation in Symptomatic Heart Failure Subjects

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| Trial Type | Prospective, randomized, parallel-controlled, multicenter clinical evaluation of the MitraClip device for the treatment of clinically significant functional mitral regurgitation in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group). |
| Sponsor | Evalve, Inc. A subsidiary of Abbott Vascular Inc. 4045 Campbell Avenue Menlo Park, CA 94025 USA |
| Enrollment/Randomization Service | Medidata RAVE |
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Compliance Statement:

This trial will be conducted in accordance with this Protocol/Clinical Investigational Plan, the Declaration of Helsinki, applicable good clinical practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812, OUS ISO14155) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the trial will be approved by the appropriate Institutional Review Board (IRB)/ Medical Ethics Committee (MEC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, Health Canada)


(Signature)

Gary Johnson
Vice President, Clinical, Regulatory & HEOR
Abbott Vascular

Clinical Trial Summary

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| Trial Name and Number | <p><u>C</u>ardiovascular <u>O</u>utcomes <u>A</u>ssessment of the MitraClip <u>P</u>ercutaneous <u>T</u>herapy for Heart Failure Patients with Functional MR (The COAPT Trial)</p> <p>CIP No. 11-512</p> |
| Investigational Device | MitraClip System |
| Title | <p><u>C</u>ardiovascular <u>O</u>utcomes <u>A</u>ssessment of the MitraClip <u>P</u>ercutaneous <u>T</u>herapy for Heart Failure Patients with Functional MR (The COAPT Trial)</p> |
| Objective | <p>To evaluate the safety and effectiveness of the MitraClip System for the treatment of moderate-to-severe or severe functional mitral regurgitation (FMR) in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site’s local heart team as not appropriate for mitral valve surgery. This randomized controlled trial will provide the opportunity to strengthen or add labeling claims regarding safety and clinical benefits of the MitraClip System for symptomatic heart failure patients with moderate-to-severe or severe functional mitral regurgitation.</p> |
| Design | <p>Prospective, randomized, parallel-controlled, multicenter clinical evaluation of the MitraClip device for the treatment of clinically significant functional mitral regurgitation in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site’s local heart team as not appropriate for mitral valve surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group). Randomization will be stratified by study site and cardiomyopathy etiology (i.e. ischemic or non-ischemic).</p> |

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| <p>Key Inclusion Criteria</p> | <ul style="list-style-type: none"> • Symptomatic functional MR ($\geq 3+$) due to cardiomyopathy of either ischemic or non-ischemic etiology • Subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure • Subject has had at least one hospitalization for heart failure in the 12 months prior to subject registration and/or a corrected BNP ≥ 300 pg/ml or corrected NT-proBNP ≥ 1500 pg/ml • New York Heart Association (NYHA) Functional Class II, III or ambulatory IV • Surgery will not be offered as a treatment option and medical therapy is the intended therapy for the subject • Left Ventricular Ejection Fraction (LVEF) is $\geq 20\%$ and $\leq 50\%$ • Left Ventricular End Systolic Dimension (LVESD) is ≤ 70 mm |
| <p>Key Exclusion Criteria</p> | <ul style="list-style-type: none"> • Untreated clinically significant coronary artery disease requiring revascularization • Coronary artery bypass grafting (CABG) within prior 30 days • Percutaneous coronary intervention within prior 30 days • Tricuspid valve disease requiring surgery • Aortic valve disease requiring surgery • Chronic Obstructive Pulmonary Disease (COPD) requiring continuous home oxygen therapy or chronic outpatient oral steroid use • Cerebrovascular accident within prior 30 days • Severe symptomatic carotid stenosis ($> 70\%$ by ultrasound) • Carotid surgery within prior 30 days • Mitral valve orifice area < 4.0 cm² • Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR by the MitraClip |

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| <p>Primary Endpoints</p> | <p>Safety: Composite of Single Leaflet Device Attachment (SLDA), device embolizations, endocarditis requiring surgery, Echocardiography Core Laboratory confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery at 12 months</p> <p>Effectiveness: Recurrent heart failure (HF) hospitalizations through 24 months (analyzed when the last subject completes 12 months of follow-up)</p> |
| <p>Secondary Endpoints</p> | <p>Secondary Safety:</p> <ul style="list-style-type: none"> • Composite of death (all-cause), stroke, myocardial infarction (MI), or non-elective cardiovascular surgery for device related complications at 30 days post-procedure in the Device group • All-cause mortality at 12 months <p>Secondary Effectiveness:</p> <ul style="list-style-type: none"> • Mitral Regurgitation (MR) severity at 12 months • Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 12 months over baseline • Change in quality of life (QoL) at 12 months over baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) • Change in Left Ventricular End Diastolic Volume (LVEDV) at 12 months from baseline • New York Heart Association (NYHA) Functional Class I/II at 12 months • Hierarchical composite of death and recurrent HF hospitalization (analyzed when the last subject completes 12 months of follow-up) • Recurrent hospitalizations - all-cause (analyzed when the last subject completes 12 months of follow-up) |

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| <p>Additional Endpoints</p> | <p>Device or Procedure-Related Adverse Events: Adverse events that are adjudicated by the Clinical Events Committee as probably, possibly or definitely device and/or procedure related, regardless of temporal relationship to the MitraClip procedure. Examples of device-related adverse events are:</p> <ul style="list-style-type: none"> • Myocardial perforation • Single Leaflet Device Attachment • Embolization of the MitraClip device or MitraClip System components • Iatrogenic atrial septal defect • Mitral valve stenosis • Need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device <p>Device and Procedure-Related Endpoints: The following device and procedure-related acute endpoints will be reported for the Device group:</p> <ul style="list-style-type: none"> • Implant Rate: defined as the rate of successful delivery and deployment of the MitraClip device(s) with echocardiographic evidence of leaflet approximation 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 duration: defined as the duration of exposure to fluoroscopy during the MitraClip procedure |
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| <p>Additional Endpoints (Continued)</p> | <p>Echocardiographic Endpoints: The following echocardiographic endpoints will be reported for the Device and Control groups at baseline, discharge (or 30 days if discharge echocardiogram is not available), 6 months, 12 months, 24 months and then yearly through 5 years. For continuous variables, change from baseline to each follow-up will also be reported:</p> <ul style="list-style-type: none"> • MR Severity Grade • Effective Regurgitant Orifice Area • Regurgitant Volume • Regurgitant Fraction • Left Ventricle 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 • Mean Mitral Valve Gradient • Systolic Anterior Motion of the mitral valve (present or absent) • Cardiac Output • Forward Stroke Volume |
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| <p>Additional Endpoints (Continued)</p> | <p>Clinical Endpoints: The following clinical endpoints will be reported for the Device and Control groups:</p> <ul style="list-style-type: none"> • Kaplan-Meier freedom from the components of the primary safety composite at 12 months, 24 months and yearly through 5 years (Device group only) • Kaplan-Meier freedom from the primary safety composite at 24 months and yearly through 5 years (Device group only) • Kaplan-Meier freedom from all-cause mortality at 12 months, 24 months and yearly through 5 years • Kaplan-Meier freedom from: (1) cardiovascular mortality (2) the first HF related hospitalization (3) the first cardiovascular hospitalization (4) the first HF related hospitalization or all-cause mortality at 12 months and 24 months and then yearly through 5 years • NYHA Functional Class at baseline, 30 days, 6 months, 12 months, 24 months and then yearly through 5 years • 6MWD at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up) • KCCQ QoL scores at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up) • SF-36 QoL scores at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up) • Mitral valve surgery (including type of surgery), new use of CRT, new use of single or dual chamber pacemaker, permanent LVAD implant, heart transplant, additional MitraClip device intervention in Device group or <i>de novo</i> MitraClip device intervention in Control group, including reason for intervention through 5 years • Responder analysis for 6MWD, where responder is defined as alive and experiencing an improvement of 24 meters and 50 meters (difference in proportion of responders between Device and Control groups) at 12 months and 24 months • Responder analysis for LVEDV Index, where responder is defined as alive and experiencing an improvement of 12 ml/m² (difference in proportion of responders between Device and Control groups) at 12 months, 24 months and then yearly through 5 years • Responder analysis for QoL (KCCQ), where responder is defined as alive and experiencing an improvement of 5 points (difference in proportion of responders between Device and Control groups) at 12 months and 24 months |
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| <p>Additional Endpoints (continued)</p> | <ul style="list-style-type: none"> • Each subscale for QoL (KCCQ) (difference in means between Device and Control groups) at 12 months and 24 months • Length of index hospitalization for MitraClip procedure (Device group) • Number of hospitalizations and reason for hospitalization (i.e., heart failure, cardiovascular, non-cardiovascular) at 12 months and 24 months in each of the Device and Control groups • Number of days alive and out of hospital from the time of randomization (difference in medians between Device and Control groups) to 12 months, 24 months and then yearly through 5 years • Number of days hospitalized from the “Treatment” visit (difference in medians between Device and Control groups) at 12 months, 24 months and then yearly through 5 years • Proportion of alive time in hospital will be summarized and compared between Device and Control groups at 12 months, 24 months and then yearly through 5 years • Proportion of subjects living in the baseline location at 12 months, 24 months and then yearly through 5 years • Mitral valve replacement rates will be summarized and compared between Device and Control groups at 12 months, 24 months and then yearly through 5 years • New onset of permanent atrial fibrillation at 12 months, 24 months and then yearly through 5 years • Mitral stenosis at 12 months, 24 months and then yearly through 5 years • Clinically significant atrial septal defect (ASD) that requires intervention at 12 months, 24 months and then yearly through 5 years • Device-related complications in Device group subjects and Control group subjects who undergo the MitraClip procedure through 5 years • BNP (Brain Natriuretic Peptide) or NT-proBNP (N-terminal prohormone of Brain Natriuretic Peptide) levels at baseline, 30 days and 12 months • Modified Rankin Scale Score at baseline, 30 days, 6 months, 12 months • Major bleeding at 30 days • Prolonged ventilation at 30 days |
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| <p>Additional Endpoints (continued)</p> | <ul style="list-style-type: none"> • Average dosages of Guideline Directed Medical Therapy (GDMT) at baseline, 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years • The number and reasons for (1) any changes in GDMT and GDMT dosage from baseline at 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years and (2) any changes in GDMT from baseline that result in a greater than 100% increase or greater than 50% decrease in dose at 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years • Peak VO₂ from cardiopulmonary exercise testing (CPX) in the subset of patients participating in the CPX sub-study at baseline and 12 months |
| <p>Sample Size / Targeted Number of Subjects to Receive Study Device</p> | <p>Approximately 610 subjects will be randomized with approximately 305 subjects targeted to receive the study device.</p> <p>Up to an additional 150 roll-in subjects, up to 3 per site, may be treated by operators without prior or recent experience using the MitraClip device to gain hands-on experience before randomizing subjects in the trial.</p> |
| <p>Subject Follow-up</p> | <p>All subjects will be scheduled for a “Treatment” visit. At the “Treatment” visit, Device group subjects will undergo the MitraClip procedure and Control group subjects will be seen by a Heart Failure specialist for a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications.</p> <p>Subjects will have required follow-up evaluations at these time points post-“Treatment” visit: 1-week (phone contact), 30 days, 6 months, 12 months, 18 months, 24 months, and annually thereafter through 5 years</p> |
| <p>Primary Analytical Population</p> | <p>The primary safety analysis set will consist of all Device group subjects in whom the MitraClip procedure is attempted. The primary effectiveness analysis set will consist of the Intention-to-Treat (ITT) randomized population. This analysis set is defined as all subjects who are registered. Subjects will be considered registered when informed consent has been obtained and they have been randomized to either the Device group or the Control group.</p> |

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| Safety Monitoring | The Data Monitoring Committee (DMC) will monitor the safety of subjects from subject registration to the required follow-up on an on-going basis. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC charter. |
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1 Introduction

The purpose of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR (COAPT) Trial is to evaluate the safety and effectiveness of the MitraClip System for the treatment of moderate-to-severe or severe functional mitral regurgitation (FMR) in symptomatic subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group).

As the Sponsor of this clinical trial, Abbott Vascular has the overall responsibility for the conduct of the trial, including assurance that the trial will be performed according to this Clinical Investigational Plan and US Food and Drug Administration (FDA) and Health Canada regulations. Abbott Vascular will have direct and indirect responsibilities for day-to-day trial management and may delegate responsibilities for some trial management activities to a Contract Research Organization (CRO).

This Clinical Investigational Plan describes the requirements for the COAPT Trial.

2 Background Information

The MitraClip System was developed as a percutaneous technology to provide an option for treatment of patients with significant mitral regurgitation (MR). The MitraClip System has been in clinical use since July 2003. The MitraClip System received CE approval in 2008 and is approved and commercially available in over 40 countries. As of August 30, 2013, more than 10,000 patients have undergone the MitraClip procedure worldwide.

2.1 MitraClip Clinical Program

Over the last 10 years, the Sponsor has collaborated with FDA to develop robust clinical trials to establish the safety and effectiveness of the MitraClip device. More than 2,000 patients have been enrolled in clinical trials as of August 30, 2013, of whom 1,200 have undergone the MitraClip procedure in the US Clinical Trial Program (**Figure 1**).

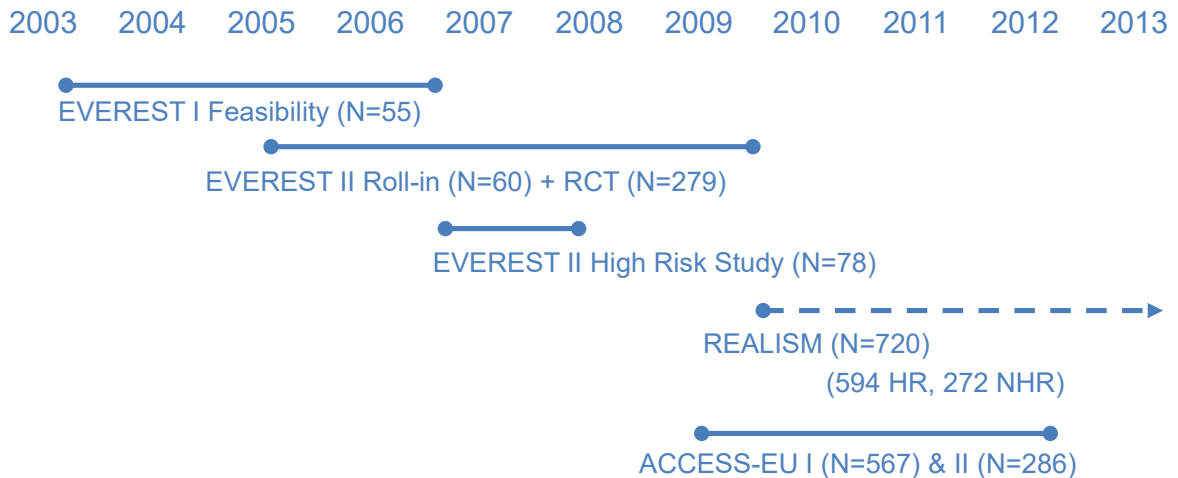


Figure 1: Timeline for Clinical Trials with the MitraClip System

Early in the Clinical Trial Program, a randomized comparison of the MitraClip System to the standard of care for the reduction of MR was considered necessary to demonstrate the safety and effectiveness of the MitraClip device. Per the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease¹ (“ACC/AHA Guidelines”), the recommended treatment for moderate-to-severe (3+) or severe (4+) MR is mitral valve surgery for many patients. The EVEREST II randomized controlled trial (RCT) therefore compared the MitraClip System to mitral valve repair or replacement surgery in patients who were indicated for and could undergo mitral valve surgery.

Due to the innovative nature of the device and procedure, the safety of the MitraClip procedure and the effect of the MitraClip device on clinical outcomes were unclear or unknown at the time the RCT was designed. Examples of these unknowns included the ability of the device to successfully capture and coapt the leaflets; safety of the procedure and the device; adequacy and durability of MR reduction; impact of MitraClip implant on subsequent mitral valve surgery; and durability and clinical benefit experienced by patients with residual MR of 2+ or less. After careful consideration of these challenges, the EVEREST II RCT was designed and conducted to collect data to evaluate procedural success, safety of the procedure in comparison to mitral valve surgery, durability of MR reduction through 12 months and 24 months in comparison with mitral valve surgery, clinical benefit of the MitraClip implant in comparison with mitral valve surgery, and type of surgery post-MitraClip procedure.

¹ Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease), JACC. 2008;52:e1-142.

The Clinical Trial Program was expanded when the EVEREST II Investigational Device Exemption was amended to add the High Risk single-arm self-controlled study contemporaneous with the initiation of a dual-arm pivotal trial for another percutaneous valve device (TAVR). The High Risk study was designed to evaluate the performance of the MitraClip System in patients who were too high risk for mitral valve surgery as determined by a cardiothoracic surgeon. EVEREST II High Risk (HR) patients were screened concurrent with enrollment in the RCT and patients were treated in the arm in which they were eligible (RCT or HR). After the RCT and HR trials were fully enrolled, a continued access study of the MitraClip System (REALISM) was approved and the study began enrolling patients in 2009. The REALISM Study consists of two arms, one arm for RCT eligible (non-high surgical risk) patients and one arm for HR eligible (high surgical risk) patients. The REALISM Study stopped enrolling in the non-high surgical risk arm in late 2011.

In 2008, after the MitraClip device received CE mark, the ACCESS EU post-approval study was initiated to study the use of the MitraClip System in patients treated in the commercial setting (“commercial use patients”) in Europe. In September 2011, the ACCESS-EU II Study was initiated to continue to study patients treated in commercial use in the EU with Echocardiography Core Laboratory adjudication of baseline and follow-up echocardiograms. As of August 30, 2013, more than 9,000 patients have been treated under the CE mark with acute procedural results available for all patients.

2.2 Results

The results presented in this section are a brief summary of results previously reported in PMA P100009 and its amendments. The clinical data and reports supporting these results are on file at Abbott Vascular and available upon request. These results have been updated through August 30, 2013 and will be updated as required in subsequent Clinical Investigational Plan amendments.

2.2.1 EVEREST I Trial

The EVEREST I trial (N=55) demonstrated evidence of the feasibility of the percutaneous approach utilizing the MitraClip System. The trial met its primary endpoint, demonstrating that the MitraClip System was safe and mechanistically feasible, which allowed for the design and initiation of the EVEREST II pivotal trial. The last patient has completed 5-year follow-up and the study is now closed.

2.2.2 EVEREST II RCT

The EVEREST II RCT (N = 60 Device roll-in, N = 184 Device randomized and N = 95 Control randomized) was conducted in patients who were indicated for and could undergo mitral valve surgery. The trial enrolled both degenerative (DMR) and functional (FMR) MR

etiologies (73% DMR, 27% FMR). The trial was intended to demonstrate superiority of safety of MitraClip balanced against reduced effectiveness when compared to mitral valve repair or replacement surgery (mitral valve replacement in the Control arm was not considered a failure). Both primary safety and effectiveness endpoints were met. Significant and meaningful clinical benefits were observed as follows:

- Superiority of safety compared to mitral valve surgery
- Reduction of MR to 2+ or less was achieved in a majority of patients in both arms, and was durable through 2 years
- Degree of MR reduction was lower in the MitraClip arm than surgery arm
- Reduction in left ventricular (LV) size was demonstrated in both MitraClip and surgery groups, despite a smaller degree of acute MR reduction with the MitraClip as compared with mitral valve surgery
- Similar improvements in NYHA Functional Class compared to mitral valve surgery
- Similar improvements in SF-36 Quality of Life compared to mitral valve surgery
- Shorter ICU time, hospital length of stay and requirement for nursing or rehabilitation care post hospitalization compared to mitral valve surgery

Additionally, the clinical benefits observed in patients with functional MR etiology were consistent with those observed in patients with degenerative MR etiology.

The results of the EVEREST II RCT through 2 years have recently been published in *The New England Journal of Medicine*.² On an intention to treat basis, the MitraClip approach has an early safety advantage, and 78% of patients in the device arm were free from surgery at two years with similar clinical benefit compared to surgery. There was no incidence of mitral stenosis, device embolization or device migration in the EVEREST II RCT. Sustained reduction in mitral regurgitation was observed, although not quite to the extent of surgery as measured by a core laboratory with established echocardiographic techniques. Continued reduction in left ventricular (LV) volumes and dimensions were observed in both MitraClip and surgery groups, although diastolic volumes were reduced to a greater degree post-surgery. Symptomatic benefit, as evidenced by improvements in NYHA Functional Class and Quality of Life measures for patients in the MitraClip device arm, was at least as good as surgery. The authors concluded that although percutaneous repair was less effective at reducing MR than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. The authors also concluded the data

² Feldman T, Foster E, Glower DG, Kar S, Rinaldi MJ, Fail PS, Smalling, RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, and Mauri L, for the EVEREST II Investigators. Percutaneous Repair or Surgery for Mitral Regurgitation, *New Engl J Med*. 2011;364:1395-1406.

demonstrate a place for the MitraClip device as a therapeutic option for selected patients with mitral regurgitation.

2.2.3 EVEREST II High Risk Registry (HRR) Study

Patients enrolled in the EVEREST II HRR Study were considered high surgical risk if the cardiothoracic surgeon at the investigational site assessed a predicted surgical mortality for mitral valve surgery of $\geq 12\%$ based on either:

- I) STS (Society of Thoracic Surgeons) mortality risk $\geq 12\%$, or
- II) The presence of at least one of the following:
 - 1) Porcelain aorta or mobile ascending aortic atheroma
 - 2) Post-radiation mediastinum
 - 3) Previous mediastinitis
 - 4) Functional MR with EF $< 40\%$
 - 5) Over 75 years old with EF $< 40\%$
 - 6) Prior re-operation with patent grafts
 - 7) Two or more prior chest surgeries
 - 8) Hepatic cirrhosis
 - 9) Three or more of the following STS high risk factors:
 - i. Creatinine > 2.5 mg/dL
 - ii. Prior chest surgery
 - iii. Age over 75
 - iv. EF $< 35\%$

The trial enrolled both degenerative and functional MR etiologies (41% DMR, 59% FMR).

The primary safety endpoint of the EVEREST II HRR Study was procedural mortality at 30 days or prior to discharge, whichever was longer. The observed procedural mortality was statistically significantly lower than the predicted surgical mortality, thus the trial met the primary endpoint of lower procedural mortality than predicted for surgery.

For this high surgical risk population with limited options, safe reduction of MR is clinically meaningful, as observed in the following endpoints:

- Reduction of MR to 2+ or less can be achieved in a majority of patients and is durable through 2 years
- Improvements in NYHA Functional Class and SF-36 Quality of Life
- Reduction in left ventricular size
- Significant decrease in the rate of hospitalization for heart failure after treatment with the device
- Reduced mortality for high surgical risk patients compared to predicted mortality from the STS database and publications
- Shorter ICU time, hospital length of stay and requirement for nursing or rehabilitation care post hospitalization compared to mitral valve surgery in non-high risk surgical patients
- Mortality at 12 months was within the range expected based on medical therapy and surgical literature

2.2.4 EVEREST II REALISM Continued Access Study

There are two groups (High Risk and Non-High Risk) in the REALISM Continued Access Study. The REALISM study began enrollment in 2009. As of August 30, 2013, 272 and 594 patients have been respectively enrolled in the Non-High Risk and High Risk arms of REALISM. Enrollment of the Non-High Risk arm of the REALISM study is complete with a total enrollment of 272 patients and follow-up through 5 years is ongoing. The High Risk arm of the REALISM study is currently enrolling. An additional 66 patients have been treated as Compassionate Use or Emergency Use cases to date. The results reported in the Non-High Risk and High Risk arms of the ongoing REALISM Study are consistent with the results reported for the RCT and HRR Study, respectively.

2.2.5 ACCESS-EU Study

The purpose of the ACCESS-EU Study was to gain information regarding the use of the MitraClip System in Europe with respect to health economics and clinical care, and to provide further evidence of the safety and effectiveness of the MitraClip System in a post-market setting. The results observed in this study are consistent with those observed in the

US clinical trials. The following results were observed in a 12-month publication on a cohort of 567 ACCESS-EU Phase-1³ patients:

- A majority (78.9%) of patients were free from MR > 2+ at 12 months compared to 3.1% at baseline
- A majority (71.4%) of patients had NYHA Class I/II at 12 months compared to 17.8% at baseline
- Clinically and statistically significant improvement (59.5 meters) in 6 Minute Walk Distance (6MWD) at 12 months compared to baseline
- Clinically and statistically significant improvement in quality of life (13.5 points) as measured by the Minnesota Living with Heart Failure (MLWHF) questionnaire at 12 months as compared to baseline

The ACCESS-EU Phase II Study started enrolling in September 2011, and includes an Echocardiography Core Laboratory assessment of study echocardiograms. A total of 286 patients were enrolled in this study. The ACCESS-EU Phase II Study has been recently closed by the Sponsor. No data have yet been reported.

2.2.6 Results in High Surgical Risk Patients

In December 2011, data from the EVEREST II HR Study (N = 78 patients with 2 years of follow-up) and the EVEREST II REALISM Continued Access High Risk arm (133 patients with 1 year of follow-up) were pooled as described in the REALISM protocol and reported to FDA in support of a high surgical risk indication (hereafter referred to as EVEREST High Risk Cohort, N = 211). These patients had a large range of co-morbidities that elevated their risk of surgical mortality. Approximately 2/3 of patients in this cohort had functional MR etiology.

Procedural results in high surgical risk patients who underwent the MitraClip procedure are very favorable even when compared to results in non-high risk patients who underwent mitral valve surgery. Procedural mortality was significantly lower than the predicted surgical mortality. EVEREST High Risk Cohort patients undergoing the MitraClip procedure had shorter anesthesia durations, post-procedure ICU/CCU/PACU duration and post-procedure hospital stay, and were discharged home without home healthcare more often than the non-high risk Control patients who underwent mitral valve surgery in the EVEREST II RCT.

³ Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W, Percutaneous Mitral Valve Interventions in the Real World: Early and One Year Results From the ACCESS-EU, a Prospective, Multicenter, Non-Randomized Post-Approval Study of the MitraClip® Therapy in Europe, *J Am Coll Cardiol*. 2013;62:1052-61.

To provide perspective on the procedural mortality results on this cohort of patients, AV compared data collected from the high surgical risk patients to the following:

- medical therapy and surgical literature for patients with MR
- retrospectively gathered Concurrent Control⁴ consisting of patients who were screened for the EVEREST II HR Study, but did not enroll
- a single center analysis of mortality for high risk patients with a diagnosis of any grade of MR (mild to severe) who underwent non-surgical management (Ohio State University (OSU) Cardiac Database)
- a single center analysis of mortality for a propensity matched cohort of high risk patients with a diagnosis of moderate-to-severe or severe MR (Duke University Medical Center) who underwent non-surgical management

Procedural (30 day) mortality in EVEREST High Risk Cohort patients was:

- lower than in-hospital mortality reported in the literature in elderly patients undergoing mitral valve surgery
- statistically significantly lower than the predicted surgical mortality, and comparable with that observed in high surgical risk patients in the Concurrent Control (no MitraClip)
- consistent with 30-day mortality observed in high surgical risk patients post-diagnosis of any MR who underwent non-surgical management from the Ohio State University Cardiac database
- comparable to 30-day mortality observed in high surgical risk patients post-diagnosis of moderate-to-severe or severe MR who underwent non-surgical management from the Duke University Medical Center

A low rate of major adverse events (MAE)⁵ was also noted at 30 days. The MAE rate in the EVEREST High Risk Cohort was much lower than that in the non-high risk Control patients who underwent mitral valve surgery in the EVEREST II RCT. These results support the

⁴ The Concurrent Control consists of patients who were screened for the EVEREST II HR Study and met the high surgical risk and MR severity criteria, but did not enroll. Abbott Vascular retrospectively gathered data on this Concurrent Control (N = 36) to assess 30 day and 12 month mortality. A majority of these patients (31 of 36) remained on medical therapy through 12 months.

⁵ MAE is defined as a combined clinical endpoint of death (all cause), myocardial infarction, 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 transfusion of 2 or more units of blood.

MitraClip as a safe procedure in these high surgical risk patients with extensive baseline co-morbidities.

High surgical risk patients with untreated clinically significant MR are highly symptomatic, have a high rate of heart failure hospitalizations, poor quality of life and impaired functional capacity. EVEREST High Risk Cohort patients treated with the MitraClip experienced immediate (post-procedure) clinically and statistically significant improvements in quality of life, heart failure symptoms, functional capacity and left ventricular volumes and dimensions, which were sustained through 12 months. These patients also experienced substantially lower rate of heart failure hospitalizations in the 12 months post-MitraClip procedure than in the preceding 12 months.

The consistent improvement across the multiple measures observed post-treatment with the MitraClip device are expected benefits of mechanical reduction of MR. Similar clinical benefits have been observed in non-high risk patients treated surgically for MR.

Although there is expectation for only a modest reduction in long-term mortality from the MitraClip, any clinical benefit with the MitraClip device must be balanced with the long-term safety of the device, i.e., no elevated risk for long-term mortality. It is therefore important to assess 12-month mortality in symptomatic patients treated with the MitraClip that are extremely high risk for mitral valve surgery. Since no parallel control was included in the EVEREST II high risk studies, long-term mortality outcomes in the EVEREST High Risk Cohort were assessed against the same comparators as those described for 30-day mortality.

The 12-month mortality rate in the EVEREST High Risk patients (N = 211) was 24%. **Figure 2** places the 12-month mortality rate in EVEREST High Risk patients in context with the comparators assessed.

This figure shows a high rate of mortality at 12 months with either mitral valve surgery or medical therapy, as expected in an elderly population with multiple co-morbidities in addition to MR. The 12-month mortality post-MitraClip implant in the EVEREST High Risk Cohort is not excessive in comparison with that reported in the literature, the Concurrent Control, and the Ohio State University Cardiac database, and is accompanied by substantial clinical benefits. In a propensity matched cohort of 127 of 211 EVEREST High Risk patients, mortality was reduced by 30% in comparison with high surgical risk patients with moderate-to-severe or severe MR in the Duke University database who underwent non-surgical management.

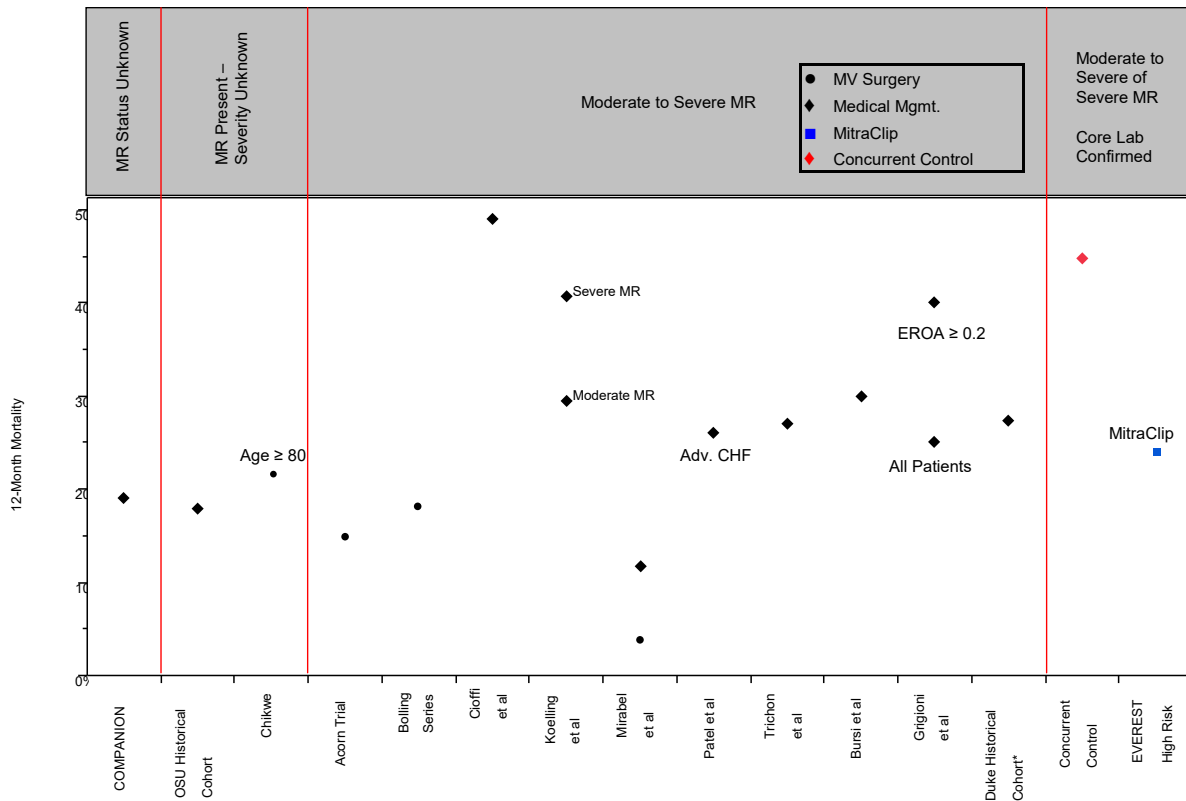


Figure 2 12-Month Mortality in EVEREST High Risk Patients and Comparators
 (Reproduced from Integrated High Surgical Risk Report submitted in PMA P100009/A016)

2.3 Rationale to Conduct the COAPT Trial

Multiple clinical trials in a large number of patients provide scientific data on the safety and effectiveness of the MitraClip System. The results of these trials provide evidence for significant clinical benefit with relatively low risk of excessive peri-procedural or long-term mortality. A large volume of data has been collected on the MitraClip device (1,270 patients treated in US clinical trials, of which 705 were high surgical risk).

In July 2013, Abbott Vascular submitted an amendment (P100009/A022) reporting safety and effectiveness results in 127 patients from the EVEREST II HRR and REALISM High Risk studies who had degenerative mitral regurgitation and were at prohibitive risk for mitral valve surgery. These data were the basis of FDA approval of the MitraClip System on October 24, 2013. In the United States, the MitraClip System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR \geq 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral

valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

An additional trial with a parallel control in heart failure patients with moderate-to-severe or severe symptomatic functional MR is in order.

Non-surgical treatment of symptomatic HF patients with functional MR is consistent with the most recent 2013 ACCF/AHA Heart Failure guidelines, in which mitral valve surgery is considered a class IIb recommendation⁶. Therefore, the Sponsor (Abbott Vascular) proposes to initiate a randomized controlled trial of moderate sample size in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery. This randomized controlled trial will provide opportunity to strengthen or add labeling claims regarding safety and clinical benefits in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group).

2.3.1 Intended Indication

The MitraClip System is intended to treat heart failure patients with symptomatic ischemic or non-ischemic functional MR ($\geq 3+$) despite optimal standard of care therapy, who have been determined by the local heart team as not appropriate for mitral valve surgery.

2.4 Summary of Investigational Device and Control Therapy

2.4.1 Name of the Investigational Device

The investigational device to be used in this trial is the MitraClip System. In this Clinical Investigational Plan, the investigational device is referred to as the "MitraClip System" or the "MitraClip device".

2.4.2 Description of the Investigational Device (MitraClip System)

The MitraClip System consists of two parts: 1) the Clip Delivery System and 2) the Steerable Guide Catheter.

The Clip Delivery System consists of three major components: 1) the Delivery Catheter 2) the Steerable Sleeve and 3) the MitraClip Device. The Clip Delivery System is introduced

⁶2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Yancy CW, Jessup M, Bozkurt B et al.; ACCF/AHA Task Force Members. J Am Coll Cardiol. 2013 62:e147-239.

into the body through a Steerable Guide Catheter and is used to advance and manipulate the implantable MitraClip Device for proper positioning and placement on the mitral valve leaflets. The Clip Delivery System is designed to deploy the implant in a way that requires multiple steps to ensure safe delivery of the device.

The MitraClip Device is a percutaneously implanted mechanical Clip. The MitraClip Device grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The MitraClip Device is placed without the need for arresting the heart or cardiopulmonary bypass. The implantable MitraClip Device is manufactured with metal alloys and polyester fabric (Clip cover) that are commonly used in cardiovascular implants. The MitraClip Device arms can be adjusted to any position from fully opened, fully inverted and fully closed. These positions are designed to allow the MitraClip Device to grasp and approximate the leaflets of the mitral valve using controls on the Delivery Catheter Handle. The MitraClip Device can be locked, unlocked and repeatedly opened and closed. The Grippers can be raised or lowered repeatedly.

The 510(k) cleared Steerable Guide Catheter (K112239), which includes a Dilator, is used to introduce the Clip Delivery System into the left side of the heart through the interatrial septum. The Steerable Guide Catheter is also used to position and orient the Clip Delivery System to the appropriate location above the mitral valve. The Dilator is used for the introduction of the Steerable Guide Catheter into the femoral vein and left atrium.

Several Class I accessories are used in conjunction with the MitraClip System including: 1) a Stabilizer, 2) a Lift 3) a Support Plate, 4) a Silicone Pad and 5) Fasteners to support and position the System during the procedure.

The MitraClip System is manufactured by Abbott Vascular Inc.

In addition to undergoing the MitraClip procedure, subjects randomized to the Device group will continue to be treated per standard of care consistent with the subject's condition during follow-up.

2.4.3 Description of the Control Group Therapy

All subjects must have been adequately treated per applicable standards, such as for coronary artery disease, left ventricular dysfunction, mitral regurgitation or heart failure (e.g., cardiac resynchronization therapy, revascularization, and/or GDMT for heart failure; see **APPENDIX A: Definitions**) and must have been determined by the site's local heart team as not appropriate for mitral valve surgery. Subjects randomized to the Control group will continue to be treated per standard of care consistent with the subject's condition during follow-up, just as the Device group, but will not undergo the MitraClip procedure for at least 24 months.

2.4.4 Procedures Involved in the Use of the Device

The procedures outlined in the approved MitraClip System Instruction for Use (IFU) must be followed in the use of this device under this Clinical Investigational Plan.

2.4.5 Training Required for the Use of the Device

Investigators will be trained in accordance with the approved MitraClip System Instruction for Use (IFU) and established MitraClip Therapy Training. Investigator training will include, but will not be limited to, the use of a heart model and demonstration unit to ensure that investigators understand the mechanics and characteristics of the MitraClip System. Sponsor staff will conduct this training and a training log will be used to document the training. Only physicians who receive all required device training and complete a training log can perform the MitraClip procedure under this Clinical Investigational Plan.

2.4.6 Investigational Device Accountability

Abbott Vascular, the Sponsor, is responsible for the availability and traceability of all investigational products. The Sponsor will ship devices (the MitraClip System) only to the Principal Investigator or his/her legal designee at each site. Documentation at each step of the process via a device disposition log is required. Use and final disposition of the investigational product will be reconciled on a regular basis.

The Investigator will maintain adequate records of the receipt and disposition of the investigational device, including part number and serial number, date of use, subject number and implanting physician. An Inventory/Device Accountability Log supplied by the Sponsor will be used. Upon completion of trial registration, investigators will be notified in writing. All unused investigational devices must be returned to the Sponsor when trial registration is complete (completed Inventory/Device Accountability Report will be generated for the site) or as otherwise deemed necessary (e.g., expired devices).

3 Trial Objectives

The objective of the COAPT Trial is to evaluate the safety and effectiveness of the MitraClip System for the treatment of moderate-to-severe (3+) or severe (4+) functional mitral regurgitation (FMR) in symptomatic heart failure subjects treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group). As these patients typically do not undergo surgery, the appropriate control group is non-surgical treatment for management of symptoms from MR.

The trial has two co-primary objectives, including one primary safety objective and one primary effectiveness objective. The trial also has two secondary safety objectives and several secondary effectiveness objectives.

3.1 Primary Objectives

The primary safety objective is to demonstrate that freedom from a composite of device-related complications in the Device group at 12 months is greater than a performance goal of 88%. The safety composite includes Single Leaflet Device Attachment (SLDA), device embolizations, endocarditis requiring surgery, Echocardiography Core Laboratory confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery (See **APPENDIX A: Definitions**).

The primary effectiveness objective is to demonstrate that subjects in the Device group experience a lower rate of recurrent heart failure (HF) hospitalization than subjects in the Control group. See **APPENDIX A: Definitions** for definition of HF hospitalization.

3.2 Secondary Objectives

There are two secondary safety objectives:

- To demonstrate that freedom from death (all-cause), stroke, myocardial infarction (MI), and non-elective (i.e. urgent or emergent) cardiovascular surgery for device related complications in the Device group at 30 days post-procedure is greater than 80%
- To demonstrate that the relative risk of all-cause mortality at 12 months between the Device and Control groups is less than 1.5

The secondary effectiveness objectives are to demonstrate that subjects in the Device group:

- Achieve MR reduction at 12 months to a greater extent than subjects in the Control group
- Have greater improvement in distance walked on the 6 Minute Walk Test (6MWT) at 12 months over baseline than subjects in the Control group
- Experience greater improvement in quality of life (QoL) at 12 months over baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) than subjects in the Control group
- Have larger reductions in Left Ventricular End Diastolic Volume (LVEDV) at 12 months over baseline than subjects in the Control group

- Achieve New York Heart Association (NYHA) Functional Class I/II more often at 12 months than the Control group
- Experience a lower rate of death or recurrent HF hospitalization than subjects in the Control group (hierarchical composite of death and recurrent HF hospitalization)
- Experience a lower rate of recurrent all-cause hospitalization than subjects in the Control group

4 Trial Endpoints

4.1 Primary Safety Endpoint

The primary safety endpoint is a composite of Single Leaflet Device Attachment (SLDA), device embolizations, endocarditis requiring surgery, Echocardiography Core Laboratory confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery at 12 months.

4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is recurrent heart failure (HF) hospitalizations through 24 months (analyzed when the last subject completes 12 months of follow-up).

4.3 Secondary Safety Endpoints

- A composite of all-cause death, stroke, MI, or non-elective cardiovascular surgery for device related complications in the Device group at 30 days
- All-cause mortality at 12 months

4.4 Secondary Effectiveness Endpoints

- MR severity at 12 months
- Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 12 months over baseline
- Change in quality of life (QoL) at 12 months from baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)

- Change in Left Ventricular End Diastolic Volume (LVEDV) at 12 months over baseline
- New York Heart Association (NYHA) Functional Class I/II at 12 months
- Hierarchical composite of death and recurrent HF hospitalization (analyzed when the last subject completes 12 months of follow-up)
- Recurrent hospitalizations - all-cause (analyzed when the last subject completes 12 months of follow-up)

4.5 Additional Endpoints

Labeling claims for the MitraClip device will be based on primary and secondary endpoints. Additional descriptive endpoints will also be reported as described below.

4.5.1 Device or Procedure-Related Adverse Events

Device or procedure-related adverse events are defined as adverse events that are adjudicated by the Clinical Events Committee as possibly, probably or definitely device and/or procedure-related, regardless of the temporal relationship to the MitraClip procedure. Device or procedure-related adverse events will be broken down into those that occur within 30 days of the procedure and those that occur after 30 days of the procedure. Examples of device-related adverse events are:

- myocardial perforation
- Single Leaflet Device Attachment
- embolization of the MitraClip device or MitraClip System components
- iatrogenic atrial septal defect
- mitral valve stenosis
- need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device

4.5.2 Device and Procedure-Related Endpoints

The following device and procedure-related acute endpoints will be reported for the Device group:

- **Implant Rate:** defined as the rate of successful delivery and deployment of the MitraClip device(s) with echocardiographic evidence of leaflet approximation 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 duration:** defined as the duration of exposure to fluoroscopy during the MitraClip procedure

4.5.3 Echocardiographic Endpoints

The following echocardiographic endpoints will be reported for the Device and Control groups at baseline, discharge (or 30 days if discharge echocardiogram is not available), 6 months, 12 months, 24 months and then yearly through 5 years. For continuous variables, change from baseline to each follow-up will also be reported:

- MR Severity Grade
- Effective Regurgitant Orifice Area
- Regurgitant Volume
- Regurgitant Fraction
- Left Ventricle 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
- Mean Mitral Valve Gradient
- Systolic Anterior Motion of the mitral valve (present or absent)
- Cardiac Output
- Forward Stroke Volume

4.5.4 Clinical Endpoints

The following clinical endpoints will be reported for the Device and Control groups:

- Kaplan-Meier freedom from the components of the primary safety composite at 12 months, 24 months and yearly through 5 years (Device group only)
- Kaplan-Meier freedom from the primary safety composite at 24 months and yearly through 5 years (Device group only)
- Kaplan-Meier freedom from all-cause mortality at 12 months, 24 months and yearly through 5 years
- Kaplan-Meier freedom from: (1) cardiovascular mortality (2) the first HF related hospitalization (3) the first cardiovascular hospitalization (4) the first HF related hospitalization or all-cause mortality at 12 months and 24 months and then yearly through 5 years
- NYHA Functional Class at baseline, 30 days, 6 months, 12 months, 24 months and then yearly through 5 years
- 6MWD at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up)
- KCCQ QoL scores at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up)
- SF-36 QoL scores at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up)
- Mitral valve surgery (including type of surgery), new use of CRT, new use of single or dual chamber pacemaker, permanent LVAD implant, heart transplant, additional MitraClip device intervention in Device group or *de novo* MitraClip device intervention in Control group, including reason for intervention through 5 years

- Responder analysis for 6MWD, where responder is defined as alive and experiencing an improvement of 24 meters and 50 meters at 12 months (difference in proportion of responders between Device and Control groups) at 12 months and 24 months
- Responder analysis for LVEDV Index, where responder is defined as alive and experiencing an improvement of 12 ml/m² (difference in proportion of responders between Device and Control groups) at 12 months, 24 months and then yearly through 5 years
- Responder analysis for QoL (KCCQ), where responder is defined as alive and experiencing an improvement of 5 points (difference in proportion of responders between Device and Control groups) at 12 months and 24 months
- Each subscale for QoL (KCCQ) (difference in means between Device and Control groups) at 12 months and 24 months
- Length of index hospitalization for MitraClip procedure (Device group)
- Number of hospitalizations and reason for hospitalization (i.e. heart failure, cardiovascular, non-cardiovascular) at 12 months and 24 months in each of the Device and Control groups
- Number of days alive and out of hospital from the time of randomization (difference in medians between Device and Control groups) to 12 months, 24 months and then yearly through 5 years
- Number of days hospitalized from the “Treatment” visit (difference in medians between Device and Control groups) at 12 months, 24 months and then yearly through 5 years
- Proportion of alive time in hospital will be summarized and compared between Device and Control groups at 12 months, 24 months and then yearly through 5 years
- Proportion of subjects living in the baseline location at 12 months, 24 months and then yearly through 5 years
- Mitral valve replacement rates will be summarized and compared between Device and Control groups at 12 months, 24 months and then yearly through 5 years
- New onset of permanent atrial fibrillation at 12 months, 24 months and then yearly through 5 years
- Mitral stenosis at 12 months, 24 months and then yearly through 5 years
- Clinically significant atrial septal defect (ASD) that requires intervention at 12 months, 24 months and then yearly through 5 years

- Device-related complications in Device group subjects and Control group subjects who undergo the MitraClip procedure through 5 years
- BNP or NT-proBNP levels at baseline, 30 days and 12 months
- Modified Rankin Scale Score at baseline, 30 days, 6 months, 12 months
- Major bleeding at 30 days
- Prolonged ventilation at 30 days
- Average dosages of GDMT at baseline, 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years
- The number and reasons for (1) any changes in GDMT and GDMT dosage from baseline at 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years and (2) any changes in GDMT from baseline that result in a greater than 100% increase or greater than 50% decrease in dose at 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years

4.5.5 CPX Sub-Study Endpoint

A sub-study endpoint will be added utilizing peak VO_2 as a parameter for cardiopulmonary exercise testing (CPX). CPX testing will be conducted at baseline and 12 months on a total of at least 50 and up to 100 subjects at qualified sites. Mean changes in peak VO_2 (ml/kg/min) will be summarized at 12 months from baseline for the subset of patients who complete a CPX test at baseline and 12 months. A comparison of change from baseline between Device and Control groups will be presented. Formal hypothesis testing and multiplicity adjustments will not be performed. A p-value for the peak VO_2 endpoint will be generated for descriptive purposes.

Peak VO_2 may be assessed in conjunction with electrocardiography, hemodynamics, subject symptomatology, and other CPX testing parameters. Abnormal responses in several of these variables may serve as exercise test termination criteria and should therefore be diligently monitored in patients.⁷

Abbott Vascular will qualify relevant sites for CPX testing through an experienced core laboratory, and all patients randomized in qualified sites will be required to undergo CPX testing. A separate Cardiopulmonary Exercise Test protocol will provide details on qualification of sites for CPX testing and the conduct of the CPX test.

⁷ Gibbons RJ, Balady GJ, Timothy BJ, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol*. 2002;40:1531-40.

4.5.6 Health Economic Data

During the course of the trial, Abbott Vascular (or third party designee) will collect health economic data. This includes gathering information regarding hospitalizations for the MitraClip procedure (index or otherwise). The data required may include billing information (provided as a UB-04 form or equivalent and itemized hospital bills) for items such as hospital care, physician services, laboratory tests and diagnostic procedures. The Institution shall submit a UB-04 form or equivalent to Sponsor in connection with the 30-day eCRFs completed following a MitraClip procedure.

As in previous MitraClip clinical studies, it is anticipated that a majority of patients enrolled in the COAPT trial will be elderly U.S. Medicare beneficiaries^{8,9}. Therefore, the results from COAPT are expected to be generalizable to the Medicare population.

5 Trial Design, Scope and Duration

5.1 Trial Design

The COAPT Trial is a prospective, randomized, parallel-controlled, multicenter clinical evaluation of the MitraClip device for the treatment of clinically significant functional mitral regurgitation in symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery. Eligible subjects will be randomized in a 1:1 ratio to the MitraClip device (Device group) or to no MitraClip device (Control group). Randomization will be stratified by study site and cardiomyopathy etiology (i.e. ischemic or non-ischemic).

5.2 Number of Subjects to be Registered

Investigational sites will attempt to recruit consecutive subjects who meet trial eligibility criteria. Subjects who provide written informed consent are considered registered for the COAPT Trial upon MitraClip procedure attempt (such subjects are referred to as "roll-in" subjects) or upon randomization (such subjects are referred to as randomized subjects). Approximately six hundred and ten (610) subjects will be randomized at up to 100 investigational sites. Up to an additional 150 roll-in subjects may be treated by operators without recent or prior experience with the MitraClip device to gain hands-on experience

⁸ Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, Whitlow PL, Rinaldi MJ, Grayburn P, Mack MJ, Mauri L, McCarthy PM, Feldman T. Percutaneous Mitral Valve Repair for Mitral Regurgitation in High-Risk Patients: Results of the EVEREST II Study. *J Am Coll Cardiol* 2014;2:172-81.

⁹ Lim DS, Reynolds MR, Feldman T, Kar S, Herrmann HC, Wang A, Whitlow PL, Gray WA, Grayburn P, Mack MJ, Glower DD. Improved Functional Status and Quality of Life in Prohibitive Surgical Risk Patients With Degenerative Mitral Regurgitation After Transcatheter Mitral Valve Repair. *J Am Coll Cardiol* 2014;2:182-91.

before randomizing subjects in the trial. See **Section 6.5.1: Roll-in Subjects** for further detail on roll-in subjects. Once the site completes the roll-in phase, the randomization phase will begin. Once the randomization phase has begun, all subsequent subjects must be randomized in the trial. Roll-in subjects will not count toward the approximately 610 subject cap for randomized subjects.

5.3 Trial Duration

The trial registration period is estimated to last approximately 24 months. Investigators at any site may not register more than 15% of the total of the approximately 610 randomized subjects. There is no minimum number of subjects to be registered at any site. Subjects will have required follow-up evaluations at 1-week, 30 days, 6 months, 12 months, 18 months, 24 months, and annually thereafter through 5 years. Control group subjects will be allowed to undergo the MitraClip procedure only after completion of the 24-month follow-up visit. When all registered subjects have been followed for 5 years, or have exited the trial, the trial will be closed.

5.4 Participation of Women in COAPT

Historically, women have been under-represented in or excluded from many clinical trials. It is important to assess the burden of disease and the safety and effectiveness of the device in both sexes. The sections below describe the prevalence of valvular heart disease, in particular, mitral regurgitation, and the measures that will be taken to ensure participation of women in the COAPT trial.

5.4.1 Sex-Specific Prevalence of Valvular Heart Disease, Diagnosis and Treatment Patterns

Population-based studies demonstrated no difference in the prevalence of valvular heart disease in men and women (Nkomo et al.¹⁰). Nkomo et al. report that in the community setting, women are diagnosed with valvular heart disease less often than men. However, the Society of Thoracic Surgeons (STS) database, which reports on mitral valve surgeries between the years 2002 and 2006, had an equal representation of women and men, although women underwent mitral valve replacement at a higher rate than men (57% women; 43% men) and mitral valve repair at a lower rate than men (41% women; 59% men).

¹⁰ Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; 368: 1005–1011.

5.4.2 Proportion of Women Included in Past Studies for Target Indication

In prior US clinical trials of the MitraClip System in high surgical risk patients (EVEREST High Risk Cohort), women constituted almost 40% of patients enrolled. This representation of women is reflective of the prevalence and diagnosis of valvular heart disease in women. This high representation of women is likely due to the following factors:

- Enrollment criteria in the US clinical trials of the MitraClip System did not differentially select men or women
- Barriers to enrollment of women (e.g., fear of fetal consequences, family responsibilities which limit ability for time commitment to study follow-up, lack of understanding about differences in disease etiology and pathophysiology leading to under-diagnosis and under-referral of women, etc.) were not significant variables. The typical subject was elderly (average age = 75 years) and enrollment was likely not impacted by issues that tend to select men preferentially over women (e.g., child care or elder care needs).
- Sites in prior clinical trials were selected to have a high rate of compliance to the Clinical Investigational Plan; therefore, subjects of either sex who met the eligibility criteria of the trial were enrolled.

5.4.3 Safety and Effectiveness Outcomes by Sex

Data from previous US clinical trials of the MitraClip System in both surgical patients and high surgical risk patients indicate no difference in either safety or effectiveness outcomes between women and men, with the exception of a higher rate of transfusions ≥ 2 units in women than men.

5.4.4 Representation of Women in the COAPT Trial

It is expected that the COAPT Trial will enroll a high proportion of women consistent with the rate registered in prior US clinical trials of the MitraClip System for the following reasons:

- As with prior clinical trials, enrollment criteria for the COAPT trial do not differentially select men or women
- Barriers to enrollment of women (e.g., fear of fetal consequences, family responsibilities which limit ability for time commitment to study follow-up, lack of understanding about differences in disease etiology and pathophysiology leading to under-diagnosis and under-referral of women, etc.) are not significant variables. The typical subject is expected to be elderly (average age = 75 years) and enrollment is

not likely to be impacted by issues that tend to select men preferentially over women (e.g., child care or elder care needs)

- Sites in the COAPT Trial will be selected to have a high rate of compliance to the Clinical Investigational Plan, therefore, subjects of either sex who met the eligibility criteria of the trial will be enrolled.

5.4.5 Subgroup Analysis for Sex

Although differences in safety and effectiveness between the Device and Control groups are not expected to be impacted by sex, the statistical analysis plan specifies a subgroup analysis by sex to evaluate treatment differences in primary safety and effectiveness endpoints.

6 Clinical Trial Procedure

6.1 Site Selection

Sites will be selected after review of a recent site assessment and the qualifications of the Principal Investigator at the site.

Each site will be required to have a multidisciplinary team. The multidisciplinary team will consist of a minimum of the following representatives:

- One (1) Interventional Cardiologist
- One (1) Cardiothoracic (CT) Surgeon
- One (1) Echocardiographer
- One (1) Heart Failure specialist

The requirements for the experience of the investigators on the multidisciplinary team are detailed in **Section 6.2.1 Investigator Experience Requirements**. Sites will use best practice guidelines such as those defined in the 2013 ACCF/AHA Heart Failure guidelines to guide the management of heart failure.

Upon Sponsor's request, Institution shall provide Sponsor with a copy of Institution's STS data for Sponsor to use in connection with the Trial in order to verify the Institution's and Investigator's surgery volumes and outcomes. The Sponsor will not use the STS database for any other purpose or disclose it to any third party other than to regulatory agencies in connection with the Trial, without Institution's prior written consent.

Sites must have adequate volume of potential subjects who meet the eligibility criteria (at least 1 subject per site per month).

Sites must have appropriate facilities (including surgical back-up facilities), resources, and equipment to perform the MitraClip procedure.

6.2 Site Personnel Selection

Site investigators selected to participate in this trial will be responsible for fulfilling the clinical trial requirements specified in this Clinical Investigational Plan.

The Sponsor will select investigators who are qualified by training and experience to perform clinical research and to participate in the investigation. The following criteria will be used to select investigators for participation in this clinical trial:

- The Principal Investigator is qualified by training and expertise as a Heart Failure specialist, Interventional Cardiologist, CT Surgeon, or Echocardiographer.
- Each site must have an investigator from each of the following specialties: Heart Failure, Interventional Cardiology, CT Surgery, and Echocardiography.
- Each site must have research staff trained to administer the modified Rankin Scale.
- Investigator and clinical research staff must have experience conducting Investigational Device Exemption (IDE) studies and have the resources to conduct the trial in accordance with this Clinical Investigational Plan.
- Investigators must agree to comply with this Clinical Investigational Plan, appropriate trial-related agreements (Investigator Agreement) and regulatory requirements.

All investigators will sign the appropriate trial-related agreements (Investigator Agreement) before they are added to the clinical trial.

The Local Site Heart Team, responsible for subject selection for the COAPT Trial, must consist of, at a minimum, the CT Surgeon and Heart Failure specialist investigators.

6.2.1 Investigator Experience Requirements

The CT surgeon investigator must be board certified (or equivalent) and have performed at least 25 mitral valve surgeries in the prior year or at least 40 mitral valve surgeries in the prior 2 years.

Investigators who serve as operators implanting the MitraClip device must be experienced in the transseptal technique.

Each site must have a HF specialist investigator that will meet with each potential subject to determine if the subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure (e.g., with cardiac resynchronization therapy, revascularization, and/or GDMT as appropriate; see **APPENDIX A: Definitions**). The Heart Failure specialist investigator must meet at least one of the following criteria:

- Certified by ABIM (American Board of Internal Medicine) Board in Advanced Heart Failure and Transplant Cardiology or must meet the eligibility to sit for the board
- UNOS (United Network for Organ Sharing) certification
- Director of Heart Failure/Transplant Cardiology at their institution
- Experience conducting advanced heart failure clinical trials as a principal investigator, and approved by HF specialist on the Central Eligibility Committee
- Recognition for heart failure skills in local/regional area, and approved by HF specialist on the Central Eligibility Committee
- Significant portion (at least 50%) of practice involves treating patients with heart failure, and approved by heart failure specialist on the Central Eligibility Committee
- Provides care within the context of a heart failure clinic and approved by HF specialist on the Central Eligibility Committee

See **Section 10.2 Central Eligibility Committee** for description of the role of the Central Eligibility Committee.

The responsibilities of the various roles/specialties on the multidisciplinary team at the site are summarized below:

| Role / Specialty | Responsibility |
|-----------------------------|--|
| Interventional Cardiologist | <ul style="list-style-type: none"> • Evaluates potential subjects (optional) • Performs MitraClip procedure* |
| Heart Failure Specialist | <ul style="list-style-type: none"> • Local Site Heart Team member • Evaluates all potential subjects in-person • Verifies and ensures stable GDMT at screening; examines subjects at all follow-up visits, including assessment of continued GDMT • Presents potential subjects to Central Eligibility Committee |
| CT Surgeon | <ul style="list-style-type: none"> • Local Site Heart Team member • Evaluates all potential subjects in-person • May present potential subjects to Central Eligibility Committee |

| | |
|-------------------|--|
| Echocardiographer | <ul style="list-style-type: none"> • Evaluates potential subjects for echocardiographic eligibility criteria • Participates in the MitraClip procedure |
|-------------------|--|

** Any of the Interventional Cardiologist, HF Specialist, CT Surgeon or Echocardiographer can be a MitraClip implanter as long as they have undergone the MitraClip Therapy Training and are authorized by the Sponsor to perform the procedure*

6.3 Subject Selection

Subjects in this trial must have heart failure with moderate-to-severe (3+) or severe (4+) symptomatic functional mitral regurgitation who are treated per standard of care and who have been determined by the site’s local heart team as not appropriate for mitral valve surgery. Several mechanisms will be employed in this trial to ensure appropriate subjects are registered in the trial.

Subjects will be selected for inclusion in the COAPT Trial by a multidisciplinary team at each investigational site involving heart failure, interventional cardiology, echocardiography and cardiac surgery. Additionally, the transthoracic echocardiogram (TTE) will be assessed by the Echocardiography Core Laboratory. The independent Central Eligibility Committee will confirm that surgery will not be offered to the subject and that subject is receiving optimal therapy, including GDMT, (see **Section 10.2 Central Eligibility Committee** for more details).

6.3.1 Defining Heart Failure Patients with Functional Mitral Regurgitation

In order to be eligible for the trial, the Local Site Heart Team (at a minimum CT surgeon and the HF specialist investigators) must determine that the subject has been treated per standard of care and is not appropriate for mitral valve surgery either before or after randomization.

The HF specialist investigator must confirm that the subject is on optimal therapy i.e., subject has been adequately treated per applicable standards, such as for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure (e.g., with cardiac resynchronization therapy, revascularization and/or GDMT as appropriate; see **APPENDIX A: Definitions**).

Once the Local Site Heart Team has determined that the subject has been optimally treated and is not appropriate for mitral valve surgery, and the Echocardiography Core Laboratory has confirmed that subject meets eligibility based on transthoracic echocardiogram (TTE), the site will submit subject data to the Eligibility Committee for review. In order to qualify for the trial, the Eligibility Committee must confirm that the subject is on optimal therapy, including GDMT and that mitral valve surgery will not be offered to the subject even if the subject is randomized to the control group, consistent with his/her medical condition (see **Section 10.2 Central Eligibility Committee** for responsibilities of the Eligibility Committee). See **Figure 3** for a flow chart detailing the screening process.

6.3.2 Eligibility Criteria

Assessment of eligibility is based on medical records and interview with the candidate subject. Clinical and laboratory tests of eligibility assessments shall be per site standard. If a specific test required to determine subject's eligibility is not included in site's standard tests, the test must be performed after written informed consent has been obtained from subject (or subject's legally authorized representative, if applicable). If any of the required screening assessments are conducted as part of standard of care prior to obtaining written informed consent, it is acceptable to provide the results of these previously performed tests for purposes of screening after the subject (or subject's legally authorized representative) has consented to participate in the study. See **Section 6.4 Subject Screening and Informed Consent** for additional details on subject screening and informed consent process.

6.3.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in the trial:

1. Symptomatic functional MR ($\geq 3+$) due to cardiomyopathy of either ischemic or non-ischemic etiology determined by assessment of a qualifying transthoracic echocardiogram (TTE) obtained within 90 days and transesophageal echocardiogram (TEE) obtained within 180 days prior to subject registration, with MR severity based principally on the TTE study, confirmed by the Echocardiography Core Lab (ECL). The ECL may request a transesophageal echocardiogram (TEE) to confirm MR etiology.

Note: Functional MR requires the presence of global or regional left ventricular wall motion abnormalities, which are believed to be the primary cause of the MR. If a flail leaflet or other evidence of degenerative MR is present, the subject is not eligible even if global or regional left ventricular systolic dysfunction is present.

Note: Qualifying TTE must be obtained after the subject has been stabilized on optimal therapy including GDMT and at least 30 days after:

- a) a greater than 100% increase or greater than 50% decrease in dose of GDMT
 - b) revascularization and/or implant of Cardiac Resynchronization Therapy device (CRT or CRT-D) or reprogramming of an implanted CRT or CRT-D that results in increased biventricular pacing (from $< 92\%$ to $\geq 92\%$)
2. In the judgment of the HF specialist investigator at the site, the subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure (e.g., with cardiac resynchronization therapy, revascularization, and/or GDMT; see **APPENDIX A: Definitions** for definition of GDMT). The Eligibility Committee must concur that the subject has been adequately treated.

3. The subject has had at least one hospitalization for heart failure in the 12 months prior to subject registration and/or a corrected BNP ≥ 300 pg/ml or corrected NT-proBNP ≥ 1500 pg/ml measured within 90 days prior to subject registration (“corrected” refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI above a reference BMI of 20 kg/m^2).

Note: BNP or NT-proBNP must be obtained after the subject has been stabilized on GDMT and at least 30 days after:

- a) a greater than 100% increase or greater than 50% decrease in dose of GDMT
 - b) revascularization and/or implant of Cardiac Resynchronization Therapy device (CRT or CRT-D) or reprogramming of an implanted CRT or CRT-D that results in increased biventricular pacing (from $<92\%$ to $\geq 92\%$)
4. New York Heart Association (NYHA) Functional Class II, III or ambulatory IV.
 5. The Local Site Heart Team (CT surgeon and HF specialist investigators) and the Central Eligibility Committee concur that surgery will not be offered as a treatment option and that medical therapy is the intended therapy for the subject, even if the subject is randomized to the Control group.
 6. Left Ventricular Ejection Fraction (LVEF) is $\geq 20\%$ and $\leq 50\%$ within 90 days prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI).

Note: The method must provide a quantitative readout (not a visual assessment).

7. Left Ventricular End Systolic Dimension (LVESD) is ≤ 70 mm assessed by site based on a transthoracic echocardiographic (TTE) obtained within 90 days prior to subject registration.
8. The primary regurgitant jet is non-commissural, and in the opinion of the MitraClip implanting investigator can be successfully be treated by the MitraClip. If a secondary jet exists, it must be considered clinically insignificant.
9. Creatine Kinase-MB (CK-MB) obtained within prior 14 days $<$ local laboratory ULN (Upper Limit of Normal)
10. Transseptal catheterization and femoral vein access is determined to be feasible by the MitraClip implanting investigator.
11. Age 18 years or older.

12. The subject or the subject's legal representative understands and agrees that should he/she be assigned to the Control group, he/she will be treated with medical therapy and conservative management without surgery and without the MitraClip, either domestically or abroad. If the subject would actively contemplate surgery and/or MitraClip if randomized to Control, he/she should not be registered in this trial.
13. The subject or the subject's legal representative has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group and returning for all required post-procedure follow-up visits, and has provided written informed consent.

6.3.2.2 Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria to participate in the trial:

1. Chronic Obstructive Pulmonary Disease (COPD) requiring continuous home oxygen therapy or chronic outpatient oral steroid use.
2. Untreated clinically significant coronary artery disease requiring revascularization.
3. Coronary artery bypass grafting (CABG) within 30 days prior to subject registration.
4. Percutaneous coronary intervention within 30 days prior to subject registration.
5. Transcatheter aortic valve replacement (TAVR) within 30 days prior to subject registration.
6. Tricuspid valve disease requiring surgery.
7. Aortic valve disease requiring surgery or transcatheter intervention.
8. Cerebrovascular accident within 30 days prior to subject registration.
9. Severe symptomatic carotid stenosis (> 70% by ultrasound).
10. Carotid surgery or stenting within 30 days prior to subject registration.
11. ACC/AHA Stage D heart failure.
12. Presence of any of the following:
 - Estimated pulmonary artery systolic pressure (PASP) > 70 mm Hg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the cath lab is able to reduce the pulmonary vascular resistance (PVR) to < 3 Wood Units or between 3 and 4.5 Wood Units with v wave less than twice the mean of the pulmonary capillary wedge pressure

- Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
 - Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
 - Hemodynamic instability requiring inotropic support or mechanical heart assistance
13. Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction, as assessed by site.
 14. Implant of any Cardiac Resynchronization Therapy (CRT) or Cardiac Resynchronization Therapy with cardioverter-defibrillator (CRT-D) within the last 30 days prior to subject registration.
 15. Mitral valve orifice area $< 4.0 \text{ cm}^2$ assessed by site based on a transthoracic echocardiogram (TTE) within 90 days prior to subject registration.
 16. Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR by the MitraClip. This evaluation is based on transesophageal echocardiogram (TEE) evaluation of the mitral valve within 180 days prior to subject registration and includes:
 - Insufficient mobile leaflet available for grasping with the MitraClip device
 - Evidence of calcification in the grasping area
 - Presence of a significant cleft in the grasping area
 - Lack of both primary and secondary chordal support in the grasping area
 - Leaflet mobility length $< 1 \text{ cm}$
 17. Hemodynamic instability defined as systolic pressure $< 90 \text{ mmHg}$ with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
 18. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
 19. Life expectancy < 12 months due to non-cardiac conditions.
 20. Modified Rankin Scale ≥ 4 disability.
 21. Status 1 heart transplant or prior orthotopic heart transplantation.

22. Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure.
23. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
24. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated).
25. Active infections requiring current antibiotic therapy.
26. Subjects in whom transesophageal echocardiography (TEE) is contraindicated or high risk.
27. Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically.
28. Pregnant or planning pregnancy within next 12 months.

Note: Female patients of childbearing age should be instructed to use safe contraception (e.g. intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release).
29. Currently participating in an investigational drug or another device study that has not reached its primary endpoint. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
30. Subject belongs to a vulnerable population (see **APPENDIX A: Definitions** for definition of vulnerable population) per investigator's judgment or subject has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

6.3.3 Justification for Inclusion and Exclusion Criteria

The COAPT Trial is designed to study heart failure subjects with moderate-to-severe (3+) or severe (4+) symptomatic functional mitral regurgitation who are not appropriate for mitral valve surgery.

Several eligibility criteria are defined to include symptomatic heart failure subjects who are not appropriate for mitral valve surgery. Additionally, the HF specialist investigator at the investigational site is required to examine the subject to assess the subject for appropriateness and optimization of medical and device therapy. All subjects must be evaluated by the Local Site Heart Team to confirm that the subject is on optimal therapy including GDMT and that mitral valve surgery will not be offered to the patient either at baseline or after randomization

even if the patient deteriorates, consistent with local standards of practice. Finally, to ensure consistency of criteria applied across sites to determine subject eligibility, an Eligibility Committee will review pertinent medical history to make the final determination regarding eligibility of prospective subjects (see **Section 10.2 Central Eligibility Committee** for more details). An upper limit for LV ejection fraction (LVEF) has been set at 50% to ensure inclusion of subjects with functional MR etiology. A lower limit of 20% for LVEF and an upper limit of 70mm on LV end systolic dimension have been set to exclude subjects whose LV dysfunction is so advanced that their symptoms and prognosis will be dominated by LV dysfunction rather than MR (and to exclude ventricles so large that 3 or more MitraClips may be required). To isolate the effect of the MitraClip device, eligible subjects must have been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure prior to registration. Subjects must also have received appropriate revascularization therapy for their coronary artery disease, and/or cardiac resynchronization therapy, if appropriate, at least 90 days prior to randomization.

Subjects must also have had a heart failure hospitalization or elevated BNP (corrected BNP ≥ 300 pg/ml or corrected NT-proBNP ≥ 1500 pg/ml) in the last 90 days so as to ensure a population at high likelihood of future heart failure hospitalizations is registered in the trial^{11,12,13,14}. A corrected BNP or NT-proBNP is implemented to account for obese subjects.

Subjects who are unlikely to benefit from the MitraClip intervention, have a life expectancy of less than 12 months due to non-cardiac conditions, or who have refractory heart failure requiring specialized interventions, such as implantation of a LVAD or listing for heart transplant, are excluded from the trial. As such, ACC/AHA Stage D heart failure subjects, non-ambulatory NYHA Functional Class IV subjects, subjects dependent on inotropic support, subjects with baseline modified Rankin Scale grade ≥ 4 disability and subjects with concomitant severe right heart dysfunction, tricuspid disease, or aortic valve disease are specifically excluded from the trial. Finally, subjects presenting with hypertrophic and restrictive cardiomyopathies are also excluded on the grounds that their left ventricle is less likely to reverse remodel.

¹¹ Pfister R, Diedrichs H, Schiedermaier A. Prognostic impact of NT-proBNP and renal function in comparison to contemporary multi-marker risk scores in heart failure patients. *Eur J Heart Fail* 2008; 10:315-320.

¹² Berger R, Shankar A, Fruhwald F. et al. Relationships between cardiac resynchronization therapy and N-terminal pro-brain natriuretic peptide in patients with heart failure and markers of cardiac dyssynchrony: an analysis from the Cardiac Resynchronization in Heart Failure (CARE-HF) study. *Eur Heart J* 2009; 30:2109-2016.

¹³ Olsson LG, Swedberg K, Cleland JGF. Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a β -blocker: Results from the Carvedilol Or Metoprolol European Trial (COMET) trial. *Euro J Heart Fail* 2007; 9:795-801.

¹⁴ Pocock SJ, Wand D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006; 27:65-75.

Additionally, appropriate mitral valve anatomic criteria ensure subjects are candidates for the MitraClip procedure.

6.4 Subject Screening and Informed Consent

All subjects must be screened by the site's investigator and clinical research staff, who have been trained to the Clinical Investigational Plan, to determine if the potential subject is eligible for trial registration. Potential subjects may be assigned up to two screening numbers; (assigned sequentially/chronologically) – the initial screening number on the Screening Log (Excel spreadsheet) and then the screening number through the electronic Case Report Form (eCRF) database. An accurate and up-to-date screening log of all subjects considered for the trial must be maintained and submitted to the Sponsor on a weekly basis during the trial registration period. The result of the subject screening process should be documented in the screening log to include clinical presentation route, whether the subject met eligibility criteria (and if not, which eligibility criteria were not met), whether the subject was subsequently registered, and the reason for not enrolling if the subject was not registered.

During the informed consent process, the investigator or designee, who has been trained on the Clinical Investigational Plan, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions from potential subjects. All subjects (or subjects' legally authorized representatives, if applicable) must sign and date the Institutional Review Board (IRB)/ Ethics Committee (EC) approved informed consent form prior to any clinical trial-specific procedures. No subjects belonging to a vulnerable population (see **APPENDIX A: Definitions** for definition of vulnerable population) will be registered. Obtaining the consent, provision of copy to the subject, along with date and time must be documented in the subject's medical records. The informed consent form must be signed by the investigator or designate. In addition, the signed informed consent must be kept in the subjects medical records. Sites may use a screening informed consent initially, followed by a full informed consent once the subject is deemed eligible for subject registration in the trial. The investigator or designee is responsible for advising the subject of any new information about the study or the MitraClip device that may become known during the study.

If a specific test required to determine subject's eligibility is not site standard of care, the test must be performed after written informed consent has been obtained. If any of the required screening assessments are conducted as part of standard of care prior to obtaining written informed consent, it is acceptable to provide the results of these previously performed tests for purposes of screening after subject (or subject's legally authorized representative) has provided informed consent.

An authorization for use and disclosure of the subjects' protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or the subject's legally authorized representative.

For live cases at congresses the patients need to sign a specific Live Case ICF, approved by the IRB/EC and by AV, as well as by the competent authorities (e.g., FDA), as applicable. The investigator must request AV approval prior to performing a Live Case.

The Sponsor will provide echocardiographic training to all sites and may assist in the review of screening echocardiograms to ensure conformance to echocardiographic eligibility requirements. Transthoracic echocardiograms will be submitted to the ECL for confirmation of eligibility prior to subject registration.

6.5 Pre-Randomization

6.5.1 Roll-in Subjects

The decision to identify a subject as a roll-in will depend on the level of experience of the Investigator with the device. Roll-in subjects will be designated by the Sponsor as such prior to treatment and will not undergo randomization. Sites may perform **up to** 3 roll-in procedures prior to beginning the randomization phase of the trial based on the following criteria:

- Investigators that do not have prior experience with the MitraClip device OR that have not performed a MitraClip procedure in the prior 12 months may perform up to 3 roll-in procedures upon approval from the Sponsor

The site must receive authorization from the Sponsor to enroll each roll-in case.

6.5.2 Screening and Baseline Assessments

Screening of a subject for possible inclusion in the trial may commence once a subject has been identified as symptomatic, potentially having clinically significant functional mitral regurgitation ($MR \geq 3+$). Subject's general medical eligibility must be assessed by the sites through subject's interview and subject's medical record review prior to subject registration and within the windows stipulated (see **Table 1** for more details). Standard of care tests that are performed prior to obtaining informed consents can be used to determine eligibility if those tests meet the requirements of this trial and are within the screening window.

Outlined below is the schedule of tests and assessments that need to be completed prior to registration:

Screening assessments within 180 days prior to registration:

- Transesophageal echocardiographic (TEE) images to be obtained and submitted to the Sponsor. Site must review the TEE images and confirm that subject has functional MR and suitable mitral valve anatomic criteria, without intracardiac mass, thrombus

or vegetation. Trained AV personnel may provide support to sites in reviewing TEE images.

- If the TEE is not standard of care at the site, the subject (or subject's legally authorized representative) must provide informed consent prior to the echocardiographic study.

Screening assessments within 90 days prior to registration:

- Medical history must be obtained, including review of subject's medical records.
- Subject is examined by the HF specialist investigator to assess the subject for appropriateness and optimization of medical and device therapy.
- STS Risk Score for mitral valve replacement and repair must be calculated.
- Subject has in-person consult with CT surgeon investigator. CT surgeon investigator must document in the subject's medical record that medical therapy is the intended therapy for the patient per their site's practice, even if the subject is randomized to the Control group and even if the subject deteriorates and/or the severity of MR increases.
- Subject is evaluated by the Local Site Heart Team to confirm that they are adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure. Subjects with current or prior symptoms of heart failure and reduced LVEF must be on stable GDMT recommended according to current guidelines⁶ as standard of care for heart failure therapy in the United States. See **APPENDIX A: Definitions** for definition of GDMT therapy. Additionally, the Local Site Heart Team must confirm that the subject is not appropriate for mitral valve surgery.
- NYHA Functional Class assessment.
- If subject has not had a heart failure hospitalization within the prior year, measure BNP or NT-proBNP.
- Transthoracic echocardiographic (TTE) images to be obtained and submitted to the Sponsor.
- Medical history must be obtained, including review of subject's medical records.
- A 12-lead ECG must be performed.
- After the ECL has confirmed subject eligibility, sites will be notified by Sponsor to compile and submit subject's pertinent medical history to the Eligibility Committee.

Screening and Baseline assessments within 14 days prior to randomization (may occur on the day of, but prior to, randomization) or registration (for roll-in subjects):

- Medical history must be obtained, including review of subject’s medical records.
- A physical exam including an assessment of subject’s cardiac status and vital signs measures (such as height, weight, heart rate, blood pressure and temperature) must be completed.
- Blood tests performed.
- Concomitant cardiovascular medications must be documented.
- Modified Rankin Scale must be assessed.
- A 12-lead ECG must be performed.
- Katz activities of daily living, grip strength, 15 feet walk test components of Frailty Index¹⁵ must be assessed but will not be used for screening subjects for the trial or submitted to the Eligibility Committee. Note: These assessments must be completed after the 6MWT and QoL questionnaires are completed.
- Site must reassess subject eligibility and reconfirm that the subject meets eligibility criteria. If there has been significant change in subject’s overall condition (i.e. due to recent MI, stroke, etc.), it may be necessary to update assessments completed during the screening process, such as TTE, STS risk calculation, etc.
- If site is participating in the CPX sub-study, subject must undergo a CPX test.
- The following tests must be performed by a coordinator who will not be involved in day-to-day activities of the COAPT trial and will not have access to the eCRFs. This coordinator will be designated as “blinded” study personnel, and will not have knowledge of the subject’s treatment assignment. A standardized script will be used when administering these assessments:
 - KCCQ and SF-36 QoL questionnaires must be completed by the subject;
Note: To minimize bias and undue influence, the QoL questionnaires will be completed by the subject, unless the subject is unable to complete the questionnaire on their own (in such cases a note to file must be completed to document the inability of subject to complete the questionnaire).

¹⁵ Fried LP, Tangen CM, Waltson J et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001 56:M146-M156.

- The 6-Minute Walk Test (6MWT) must be administered according to the ATS Statement: Guidelines for the Six-Minute Walk Test, Official Statement of the American Thoracic Society, approved March 2002 (See **APPENDIX E: 6 Minute Walk Test Guidelines**).
- An assessment of NYHA Functional Class must be completed.

The following screening and baseline information must be captured on the appropriate electronic Case Report Forms (eCRFs):

- Inclusion and Exclusion criteria
- Demographics (e.g., date of birth, gender, race/ethnicity)
- Informed Consent date

6.6 Subject Registration

Subjects are enrolled upon providing written informed consent. Subjects will be assigned a subject number upon MitraClip procedure attempt (see **APPENDIX A: Definitions** for definition of MitraClip procedure attempt) for roll-in subjects and upon randomization for those subjects who are randomized. Such subjects are registered in the trial.

6.7 Randomization

Before randomization:

- Echocardiography Core Lab must confirm MR severity
- Eligibility Committee must confirm that the subject is on optimal therapy including GDMT and is not appropriate for mitral valve surgery according to local site standards either at baseline or if the subject deteriorates and/or MR increases in severity during follow-up
- Site must reconfirm that subject meets eligibility criteria after Eligibility Committee approval and all baseline tests and assessments must be completed (within 14 prior to randomization)

If screening TEE shows intracardiac mass, thrombus or vegetation, or the Eligibility Committee determines subject requires additional treatment before consideration for the trial, the subject may be deferred and reconsidered for the trial, at which time the TEE must be repeated.

Subjects will be randomized or assigned as a roll-in through the eCRF database. The following baseline information must be captured for registered subjects on the appropriate eCRFs:

- Subject medical history and risk factors
- Current cardiovascular medications
- Physical measurements and vital signs (e.g. weight, height, heart rate, blood pressure and temperature)

6.8 “Treatment” Visit (Device Group or Roll-in Subjects)

For Device group or roll-in subjects, the MitraClip procedure will be performed during the “Treatment” visit. For randomized subjects, the MitraClip procedure must be completed between 1 and 14 days after randomization.

6.8.1 Anticoagulation and Antibiotic Therapy

6.8.1.1 Anticoagulation Therapy

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) is ≤ 1.7 prior to the MitraClip procedure. 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 treating physician’s discretion. If heparin is used, it should be discontinued ≥ 8 hours prior to the MitraClip procedure for subcutaneous low molecular weight heparin (LMWH) and ≥ 4 hours prior to the MitraClip procedure for intravenous unfractionated heparin (UFH).

6.8.1.2 Clopidogrel

A loading dose of clopidogrel (≥ 300 mg) is recommended within 24 hours prior to the procedure (6-24 hours prior if possible) or immediately following the procedure.

Note: A loading dose of clopidogrel may be considered even if the patient is taking clopidogrel on a daily basis either at home or in the hospital, as long as no other clopidogrel loading dose has been given within 24 hours. However, clopidogrel use is optional and its use is left to the discretion of the investigator.

Aspirin may also be used at operator discretion. If aspirin is to be used, a loading dose of 325 mg acetylsalicylic acid (ASA) may be administered either pre- or immediately post-MitraClip procedure.

6.8.1.3 Antibiotic Therapy

Administer a single dose of intravenous broad spectrum antibiotics approximately one hour prior to initiation of the procedure. The type of antibiotic is at the Investigator's discretion.

6.8.2 MitraClip Procedure

6.8.2.1 Pre-Procedural TEE

Prior to the MitraClip procedure, Device group (after randomization) and roll-in subjects must be assessed to ensure there is no significant change in subject's overall condition (e.g., stroke, MI, active infection, endocarditis, hemodynamic instability, etc. post-randomization) that would preclude treatment. If the subject has experienced any significant change that would preclude treatment, the subject must be treated and rescheduled for the MitraClip procedure as soon as possible. Subjects are required to complete an additional transesophageal (TEE) echocardiogram study within 3 days prior to the procedure to rule out the presence of intracardiac mass, thrombus or vegetation. This echocardiogram may be performed immediately preceding initiation of the MitraClip procedure. This echocardiogram will not be submitted to the ECL. If an intracardiac mass, thrombus or vegetation or other change in echocardiographic eligibility is identified in the TEE performed immediately preceding the procedure, the subject will be considered registered even if no device implant is attempted. If a thrombus is identified, the subject should be pharmacologically treated to resolve the thrombus and, if successful, the subject should be reassessed as soon as possible to undergo the MitraClip procedure. Such subjects will be considered registered even if they do not undergo the MitraClip procedure.

6.8.2.2 Pre-Procedural ECG and Physical Exam

A 12-lead ECG and physical exam should be performed within 24 hours prior to the procedure.

6.8.2.3 Baseline Activated Clotting Time

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

6.8.3 Personnel

The use of transesophageal echocardiography (TEE) requires conscious sedation or general anesthesia, depending on hospital standard practice.

If complications arise during the procedure, it may be necessary to convert to an open surgical procedure. Emergency surgical back-up should be available as per the institution's standard procedures.

The Sponsor will be available to provide technical support to answer questions regarding the function and operation of the MitraClip System.

6.8.4 Subject Preparation

Subjects will be prepared for the procedure as per the institution's standard practice for a percutaneous procedure and TEE.

Note: Prior to performing the procedure, all Investigators must also undergo documented training by the Sponsor on the MitraClip System and the Clinical Investigation Plan. In addition, all Investigators must read and understand the Instructions for Use (IFU) that accompanies the Device.

Femoral vein transseptal catheterization will be completed in accordance with the IFU.

6.8.5 Anticoagulation Therapy

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. Low molecular weight heparin and fondaparinux may not be used for procedural anticoagulation.

6.8.6 MitraClip Device Placement 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. See **APPENDIX C: Monitoring Exposure to Ionizing** for requirements for training and data gathering on ionizing radiation required per this Clinical Investigational Plan. 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 placement of one MitraClip device does not result in reduction in MR to a level deemed acceptable by the operator, then a second MitraClip device may be placed to further reduce MR. The Investigator should determine if there is adequate mitral valve orifice area to accommodate the second MitraClip device without creating mitral stenosis. In most cases a maximum of two (2) MitraClip devices will be allowed to be implanted in subjects registered in this trial. However, a third MitraClip may be used in the special circumstance when one or both of the two previous MitraClip devices have detached from one leaflet or when there is evidence of inadequate MR reduction with two MitraClip devices during either the treatment visit or follow-up.

6.9 Post-MitraClip Procedure (Device Group or Roll-in Subjects)

6.9.1 Subject Management Guidelines

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

Subjects will receive standard post-cardiac catheterization procedure care as judged appropriate by the Investigator. Subjects should be advised to limit strenuous physical activity for the first month following the MitraClip procedure or longer, as deemed appropriate by the Investigator.

6.9.2 Antibiotic Therapy

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

The Investigator should instruct all subjects who receive the MitraClip device of the need for endocarditis prophylaxis, as recommended in the *ACC/AHA 2008 Guideline Update on*

*Valvular Heart Disease: Focused Update on Infective Endocarditis*¹⁶. Subjects should 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. A prescription for endocarditis prophylaxis may be provided to the subject at discharge.

6.9.3 Antiplatelet/Anticoagulation Regimen

Following placement of the MitraClip device, anticoagulation therapy is prescribed. If a loading dose of clopidogrel was not given prior to the MitraClip procedure, it may be administered after the procedure at investigator discretion. Post-MitraClip procedure anticoagulation is 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, aspirin and clopidogrel 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 (75 mg) and/or aspirin (81 mg) is administered for 6 months or longer. If aspirin is to be used, a loading dose of 325 mg acetylsalicylic acid (ASA) may be administered either pre- or immediately post-MitraClip procedure followed by 81 mg per day for 6 months or longer at the Investigator's discretion.

6.9.4 Management of Hypertension

Subjects should have their blood pressure checked prior to discharge. Subjects should be prescribed medication as necessary following current standard of care to maintain normotensive blood pressure.

6.9.5 Vital Signs

Vital signs (i.e., weight, blood pressure, heart rate, temperature) will be obtained prior to subject discharge from the hospital.

¹⁶ Nishimura, et al. ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008; 118(8):887-894.

6.9.6 Implant Identification Card

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

6.9.7 Procedural and Discharge Data

The following MitraClip procedural information should be recorded on the appropriate eCRF(s) after implant or attempted implant of the MitraClip device:

- General procedure information
- MitraClip implant information
- Laboratory and clinical tests
- Antiplatelet/Anticoagulation medications
- Concomitant cardiovascular medications
- Fluoroscopy duration
- Adverse events
- Protocol deviations
- Device deficiency

At the Discharge visit (Discharge occurs when subject leaves the implanting hospital), the following required tests and procedures should be completed (> 16 hours post MitraClip procedure and no later than day of discharge) as outlined below, and the information should be captured on the appropriate eCRFs:

- 12-lead ECG
- Blood draw
- Brief physical exam including vital signs (weight, heart rate, blood pressure and temperature)
- Echocardiogram (TTE) - discharge TTE must be performed at least 16 hours post MitraClip procedure and no later than 24 hours post-discharge

- Modified Rankin Scale
- Adverse events
- Protocol deviations
- Device deficiency

Instructions for the TTE are provided in this investigational plan and are located in **APPENDIX B: Echocardiography Protocol.**

6.10 “Treatment” Visit (Control Group)

The “Treatment” visit in the Control group must occur between 1 and 14 days after randomization. At the “Treatment” visit, Control group subjects will be seen by the HF specialist investigator, and will undergo a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications.

6.11 Clinical Follow-up (All registered subjects)

Follow-up visits are required at 1 week (phone contact), 30 days, 6 months, 12 months, 18 months, 24 months, and annually thereafter through 5 years. For all randomized subjects, follow-up visits will be calculated from the date of the “Treatment” visit and for roll-in subjects, follow-up visits will be calculated from the date of the index procedure. Follow-up assessments can be performed at any point in the window, and should be conducted, whenever possible, by the same individual who performed the baseline tests. The subject should be followed at the investigational site where the subject was registered, and may be followed at another investigational site only with prior agreement from that site’s Investigator and from the Sponsor.

Subjects should have their blood pressure checked at each scheduled in-clinic visit. Subjects should be prescribed medication as necessary following current standard of care to maintain normotensive blood pressure.

All subjects, regardless of randomization assignment or roll-in designation, should continue to be monitored and treated per applicable standards of care consistent with the subject’s condition. All subjects must be followed by the heart failure specialist investigator at all scheduled follow-up visits. Subjects implanted with the MitraClip device must also be evaluated for device integrity. The site Principal Investigator should collaborate with the other site investigators as applicable in determining the treatment strategy for all subjects registered at their site. The electronic case report forms will document changes in treatment strategy (i.e. new use of CRT, PCI, and mitral valve surgery) and who was involved with determining changes in treatment strategy.

Study personnel administering the 6MWT and QoL questionnaires from baseline through 24 months excluding the 18-month visit and assessing NYHA Functional Class from baseline through the 5 year visit will be blinded, i.e., will not have access to the eCRF and will not have knowledge of the subject's treatment assignment. Additionally, a standardized script will be used when administering the assessments and the subject will be reminded to not reveal their treatment history to the administrator (See **Section 10.14 Measures Taken to Avoid and Minimize Bias During Study Conduct** for additional information).

To support the primary effectiveness endpoint analysis, clinical sites and all randomized subjects (or their identified contacts) will be contacted to determine each subject's survival status and date(s) of last known heart failure hospitalizations. This data sweep of death and heart failure hospitalizations will be conducted when the last randomized subject has passed the upper limit of the window for the 12-month follow-up period (i.e., 395 days after enrollment). The sweep contact is not needed for subjects who had a follow-up visit within 30 days of the sweep date, or for subjects who already completed their 24-month follow-up visit.

6.11.1 1-Week Phone Contact

All subjects will be contacted by telephone at the 1-week visit. Sites will follow a standardized script for all subjects to minimize bias. Additionally, for Device group or roll-in subjects who underwent the MitraClip procedure, the script will include a query about adverse events, including suspected skin injury.

6.11.2 30-Day, 6-Month, 12-Month, 18-Month and 24-Month Visits

During the physical examination at the 30-day follow-up clinic visit, the implanting or treating investigator shall examine the integrity of the Device group or roll-in subject's skin at or near the beam entrance site for subjects that have undergone a MitraClip procedure. At the 30-day, 6-month, 12-month, 18-month and 24-month follow-up visits, all subjects must be examined by the heart failure specialist investigator. Subjects must continue to take baseline medications without change during follow-up, unless clinically (medically) necessary. If there are any cardiovascular medication changes (including dosage changes), these changes, and the reason for change must be documented on the electronic case report form. In general, neurohormonal antagonists should not be changed. Subjects implanted with the MitraClip device must also be evaluated for device integrity. Required tests and procedures outlined below must be completed. All visits and tests must be completed even if the subject is in hospital.

- 12-lead ECG
- Blood draw

- Brief physical exam including vital signs (weight, heart rate, blood pressure and temperature)
- Echocardiogram (TTE)
- Modified Rankin Scale (Assessment of mRS should additionally be done at 90 days after onset of stroke) (not required after 12 months)
- 6-Minute Walk Test (6MWT) (not required at 18 months) – See **APPENDIX E: ATS 6 Minute Walk Test Guidelines** – must be administered by “blinded” study personnel
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment – must be administered by “blinded” study personnel
- QoL questionnaires to be completed by the subject (not required at 18 months) – must be administered by “blinded” study personnel; Note: To minimize bias and undue influence, the QoL questionnaires will be completed by the subject, unless the subject is unable to complete the questionnaire on their own (in such cases, a note to file must be completed to document the inability of subject to complete the questionnaire)
- Assess and record adverse events
- Assess and record protocol deviations

Instructions for the TTE are provided in **APPENDIX B: Echocardiography Protocol**.

6.11.3 3, 4 and 5 Year Visits

Medications should be recorded and required tests and procedures outlined below should be completed. All subjects must be examined by the heart failure specialist investigator. Subjects must continue to take baseline medications without change during follow-up, unless clinically (medically) necessary. If there are any cardiovascular medication changes (including dosage changes), these changes, and the reason for change must be documented on the electronic case report form. In general, neurohormonal antagonists should not be changed. Subjects implanted with the MitraClip device must also be evaluated for device integrity. Required tests and procedures outlined below must be completed. All visits and tests must be completed even if the subject is in hospital.

- 12-lead ECG
- Brief physical exam including vital signs (weight, heart rate, blood pressure and temperature)

- Concomitant cardiovascular medications assessment
- Echocardiogram (TTE)
- NYHA Functional Class assessment
- Assess and record adverse events
- Assess and record protocol deviations

Instructions for the TTE are provided in **APPENDIX B: Echocardiography Protocol**.

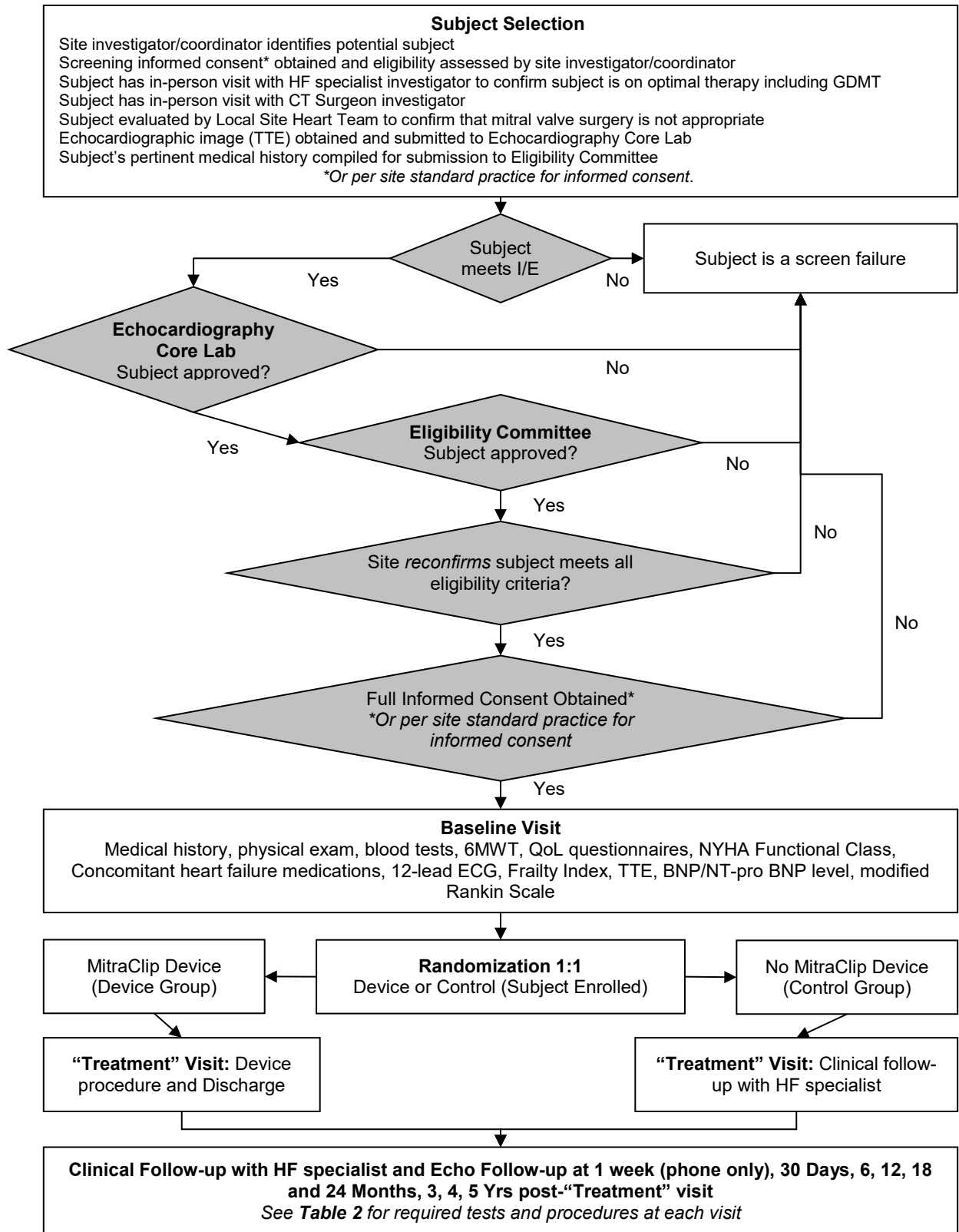


Figure 3: Trial Flowchart

After the “Treatment” visit, the investigational sites will be provided the target date and required follow-up window time-frames for each subject in the electronic data capture system. Follow-up windows are summarized in **Table 1: Follow-up Schedule* and Windows for Registered Subjects**. All data required for follow-up must be collected within the window for that scheduled visit, and not necessarily on the same day.

Table 1: Follow-up Schedule* and Windows for Registered Subjects

| Follow-Up Visit | Window Start Day | Target Day | Window Close Day | Follow up Method |
|----------------------------------|------------------|----------------|------------------|---------------------------|
| Discharge (Device group only) | NA | Discharge date | NA | In hospital or Site visit |
| 1 Week (-1 /+3 days) | 6 | 7 | 10 | Phone contact |
| 30 Days (-3 /+14 days) | 27 | 30 | 44 | Site visit |
| 6 Months (±30 days) | 152 | 182 | 212 | Site visit |
| 12 Months (-14/+30 days) | 351 | 365 | 395 | Site visit |
| 18 Months (±30 days) | 518 | 548 | 578 | Site visit |
| 24 Months (±30 days) | 701 | 731 | 761 | Site visit |
| 3 Years (±45 days) | 1051 | 1096 | 1141 | Site visit |
| 4 Years (±45 days) | 1416 | 1461 | 1506 | Site visit |
| 5 Years (±45 days) | 1781 | 1826 | 1871 | Site visit |

* Follow-up visit dates are calculated from the “Treatment visit” for randomized subjects and from the index procedure for roll-in subjects

Echocardiography images (TTE) obtained at each follow-up visit should be submitted to the Sponsor in a timely manner. The ECL will provide feedback to sites regarding quality of images obtained.

During the follow-up period, if a subject requires a cardiac procedure (i.e. MV surgery, permanent LVAD, heart transplant, additional MitraClip procedure, etc.) which may or may not result in explant of the MitraClip device, the subject will remain in the trial and continue to be followed.

Subjects who do not have a scheduled follow-up visit will be documented as having a missed visit and a Protocol Deviation will be completed. The investigator will keep a record of

documented follow-up attempts in the subject's study file. Refer to Section **10.10 Protocol Deviations** for additional information.

Table 2 provides a complete listing of required tests and procedures for all subjects through the trial follow-up period.

Table 2: Clinical Evaluation Schedule for Registered Subjects

| Items | Screening/ Baseline | Randomization Assignment (For randomized Subjects only) | Treatment Visit (Control Group) | Treatment Visit (Device Group or Roll-in) | Discharge (Device Group or Roll-in) | 1-Week Phone Contact | 30-Days ^d , 6, 12, 18, 24 Months | 3, 4, 5 Years |
|--|---|--|---------------------------------------|--|--|----------------------------|---|------------------|
| Informed Consent | X | | | | | | | |
| Medical History | X within 90 days pre-registration | | | | | | | |
| Evaluation by Local Heart Team including HF Specialist Investigator and CT Surgeon Investigator (in-person consult with HF specialist and CT Surgeon investigators is required). | X within 90 days pre-registration | | X | | | | X | X |
| Components of Frailty Index | X within 14 days pre-registration | | | | | | | |
| STS Risk Score | X within 90 days pre-registration | | | | | | | |
| Modified Rankin Scale ^a | X within 14 days pre-registration | | | | X | | X not required after 12-month visit | |
| Physical Examination & Vital Signs: (height (at Baseline only), weight, heart rate, blood pressure and temperature) | X within 14 days pre-registration | | X | X within 24 hours pre- procedure | X | | X | X |
| Concomitant Cardiovascular Medications | X | | X | X | X | | X | X |
| 12-lead ECG | X within 90 days and 14 days pre- registration | | | X within 24 hours pre- procedure | X | | X | X |
| Transthoracic Echocardiogram ^b | X within 90 days pre-registration | | | | X | | X | X |

| Items | Screening/ Baseline | Randomization Assignment (For randomized Subjects only) | Treatment Visit (Control Group) | Treatment Visit (Device Group or Roll-in) | Discharge (Device Group or Roll-in) | 1-Week Phone Contact | 30-Days ^d , 6, 12, 18, 24 Months | 3, 4, 5 Years |
|---|--|--|---------------------------------------|--|--|----------------------------|---|--------------------------------------|
| Transesophageal Echocardiogram | X within 180 days pre-registration | | | X within 3 days pre- procedure | | | | |
| Albumin | X within 14 days pre-registration | | | | | | | |
| CBC with differentials and platelet count Serum Creatinine PTT or PT or INR CK, CK-MB | X within 14 days pre-registration | | | | X | | X | |
| BNP or NT-proBNP ^c | X within 90 days pre-registration | | | | | | X | |
| 6 Minute Walk Test Quality of Life Questionnaires (KCCQ and SF-36) | X within 14 days pre-registration (by blinded study personnel) | | | | | | X (by blinded study personnel) not required at 18-month visit | |
| NYHA Functional Class | X within 90 days and 14 days pre- registration (by blinded study personnel) | | | | | | X (by blinded study personnel) | X (by blinded study personnel) |
| Inquiry of Subject Status | | | | | | X | | |
| Adverse Events | | X ^c | X | X | X | X | X | X |

^a Assessment of mRS should also be done 90 days after onset of stroke

^b TTE for the purpose of determining eligibility must be obtained after the subject has been stabilized on optimal therapy including GDMT and undergone revascularization and/or CRT, as appropriate (see **APPENDIX A: Definitions** for definition of optimal therapy and GDMT), and submitted to the ECL. A TTE must also be performed within 90 days prior to any additional MitraClip procedure or mitral valve surgery.

^c BNP or NT-proBNP must be measured after the subject has been stabilized on GDMT and undergone revascularization and/or CRT, as appropriate (see **APPENDIX A: Definitions** for definition of GDMT)

^d A 30-day visit should be performed 30 days after mitral valve surgery or MitraClip procedure in the Control group and after mitral valve surgery or additional MitraClip procedure in Device group or roll-in subjects per the requirements specified in **Section 6.13.1 30-Day Post-MitraClip Follow-up** and **Section 6.14.1 30-Day Post-Mitral Valve Surgery Follow-up**.

^e Adverse events must be collected upon trial registration for roll-in and randomized subjects

NOTE: When the last randomized subject has passed the upper limit of the window for the 12-month follow-up, subjects (or their identified contacts) will be contacted to determine survival status and date(s) of last known heart failure hospitalizations. See **Section 6.11 Clinical Follow-up (All registered subjects)** for details.

6.12 Heart-Related Office Visits

A Heart-Related Office Visit eCRF should be completed if a subject is seen for a heart-related reason at the investigational site or at any other facility. Information pertaining to adverse events, heart failure medication changes or hospitalizations, as appropriate, should also be collected.

If an echocardiographic imaging study is performed at any visit, whether or not it is a study related visit, echocardiography images should be submitted to the ECL in a timely manner.

6.13 MitraClip Intervention in Control Group Subjects or Additional MitraClip Intervention in Device Group or Roll-in Subjects

Control group subjects will not be allowed to undergo the MitraClip procedure prior to completion of the 24-month visit. MitraClip intervention in the Control group prior to the 24-month visit will be considered a major protocol deviation. Prior to MitraClip procedure attempt in a Control group subject upon completion of 24-month visit, the following must be verified:

- The primary regurgitant jet must be non-commissural, and in the opinion of the MitraClip implanting investigator can be successfully be treated by the MitraClip. If a secondary jet exists, it must be considered clinically insignificant
- Mitral valve orifice area must be $\geq 4.0 \text{ cm}^2$
- Leaflet anatomy must not preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR by the MitraClip
- No echocardiographic evidence of intracardiac mass, thrombus or vegetation

It may be necessary for a Device group or roll-in subject to undergo additional MitraClip procedures. A TTE must be performed within 90 days prior to a MitraClip procedure in either group. A 30-Day Post-MitraClip Follow-up visit must be completed 30 days (-3 /+14 days) after the additional MitraClip procedure. This visit should still be completed even if the subject is in hospital. Requirements for this visit are described in **Section 6.13.1 30-Day Post-MitraClip Follow-up**.

6.13.1 30-Day Post-MitraClip Follow-up

Requirements for the 30-day Post-MitraClip Follow-up visit are described below.

- 12-lead ECG
- Blood draw

- Brief physical exam including vital signs (weight, heart rate, blood pressure and temperature)
- Echocardiogram (TTE)
- Modified Rankin Scale (Assessment of mRS should additionally be performed at 90 days after onset of stroke)
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment
- Assess and record adverse events
- Assess and record protocol deviations

Instructions for the TTE are provided in **APPENDIX B: Echocardiography Protocol**.

6.14 Mitral Valve Surgery

For inclusion into this trial, all subjects prior to registration are deemed not appropriate for mitral valve surgery. Mitral valve surgery in either group is not allowed at any time during follow-up. Mitral valve surgery in either group will be considered a protocol deviation, unless the subject experiences a complication (e.g., endocarditis, clip detachment, or leaflet injury from the MitraClip procedure). Subjects who undergo mitral valve surgery will continue to be followed per this Clinical Investigational Plan. A TTE must be performed within 90 days prior to mitral valve surgery.

A 30-Day Post-Mitral Valve Surgery Follow-up visit must be completed 30 days (-3 /+14 days) after the mitral valve surgery. This visit should still be completed even if the subject is in hospital. Requirements for this visit are described in **Section 6.14.1 30-Day Post-Mitral Valve Surgery Follow-up**.

6.14.1 30-Day Post-Mitral Valve Surgery Follow-up

Requirements for the 30-day Post-Mitral Valve Surgery Follow-up visit are described below.

- 12-lead ECG
- Blood draw
- Brief physical exam including vital signs (weight, heart rate, blood pressure and temperature)
- Echocardiogram (TTE)

- Modified Rankin Scale (Assessment of mRS should additionally be performed at 90 days after onset of stroke)
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment
- Assess and record adverse events
- Assess and record protocol deviations

Instructions for the TTE are provided in **APPENDIX B: Echocardiography Protocol**.

6.15 Explanted MitraClip Device

The MitraClip device may be explanted during mitral valve surgery or an autopsy. If possible, fluoroscopic images with side views of the device should be obtained prior to explant. Following explant of the MitraClip device(s) during surgery, the subject will continue to be followed as defined in **Table 1: Follow-up Schedule* and Windows for Registered Subjects**. Explant information will be captured on the Mitral Valve Surgery Form or Death Form.

6.16 Subject Discontinuation

Each registered subject shall remain in the trial until the 5-year follow-up visit; however, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject's follow-up is terminated according to **Section 6.17 Early Termination of the Clinical Trial**.

Investigators should meet with the subject if there is any consideration of withdrawal. The Sponsor must be notified of subject discontinuation and the reason for discontinuation on the electronic Case Report Form (eCRF). Investigators must also report the withdrawal to their IRB/EC as defined by their institution's procedure. Discontinued subjects will not be replaced. However, if a subject withdraws from the study due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical evaluation.

6.16.1 Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up visits, and 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 follow-up visit:

A minimum of 3 telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date and initials of site personnel trying to make contact.

If these attempts are unsuccessful, a certified or registered letter with confirmed receipt should be sent to the subject.

If a subject misses one or more non-consecutive follow-up visits, these will be considered missed visits. The subject may then return for subsequent visits. If the subject misses two consecutive follow-up visits 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 presence of subject, or indirect documentation obtained via discharge letters will not be considered as subject contact.

Until trial completion, sites shall continue to obtain vital status for lost-to-follow subjects from death registries or social security index, as applicable, and document in the eCRF.

6.17 Early Termination of the Clinical Trial

The Sponsor reserves the right to discontinue this clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) include:

- Unanticipated adverse device effect (UADE) occurs and it presents an unreasonable risk to subjects.
- The Steering Committee makes a decision for the early termination of the clinical trial per Data Monitoring Committee (DMC) recommendation (such as high frequency of anticipated adverse device effects).

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

- Visiting the investigator

- Telephoning the investigator
- Corresponding with the investigator

Repeated non-compliance with the Clinical Investigational Plan 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, Sponsor may terminate the investigator's participation in the study.

6.18 Trial Completion

The trial will be completed when all subjects have either completed a 5-year follow-up visit or withdrawn from the trial. A subject is considered to have completed participation in the trial:

- if the subject is considered lost to follow-up per the above definition or
- if the subject withdraws from the clinical trial or
- if the subject has died prior to completion of 5-year follow-up or
- upon completion of 5-year follow-up

6.19 Trial Closure

Upon trial completion, the Sponsor and/or its designees will notify the sites. Trial closeout visits will be performed. All unused devices and any unused trial materials and equipment will be collected and returned to the Sponsor and/or its designees. The monitors will ensure that the investigator's regulatory files are up to date and complete, that database queries are resolved, and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include: discussing record retention requirements (refer to **Section 11.3 Site Record Retention**), device accountability, possibility of site audits, publication policy, and notifying the IRB/EC of study closure, etc.

7 Statistical Methods

There are two co-primary safety and effectiveness endpoints in this trial and several secondary safety and effectiveness endpoints.

7.1 Analysis Populations

7.1.1 Intention to Treat (ITT) Population

The Intention to Treat population will consist of all subjects randomized in the trial. All subjects will be analyzed in the group randomized regardless of the treatment actually received.

7.1.2 Per Protocol Population

The Per Protocol (PP) cohort will consist of subjects who meet all inclusion and none of the exclusion criteria for the trial, and receive the treatment as randomized. Subjects who are randomized to Device group but refuse to receive the treatment, or subjects in the Device or Control group who fail to return for the “Treatment” visit within the pre-specified window will be excluded from the Per Protocol cohort. For subjects in either group who undergo other interventions for heart failure (e.g. mitral valve surgery, LVAD/CRT implant, heart transplant), follow-up data after the date of the intervention will be excluded from analysis. Similarly, for subjects in the Control group who receive the MitraClip device, follow-up data after the date of the procedure will be excluded from analysis.

7.1.3 As Treated Population

The As Treated cohort is defined to consist of randomized subjects who receive treatment as randomized. Subjects who are randomized to the Device group but have an unsuccessful implant will be analyzed in the Device group of the As Treated cohort. Subjects who are randomized to the Device group but refuse to receive the treatment will be excluded from analyses of the As Treated cohort. For subjects who undergo other interventions for heart failure (e.g. mitral valve surgery, LVAD/CRT implant, heart transplant) in either group, follow-up data after the date of the intervention will be excluded from analysis. Similarly, for subjects in the Control group who receive the MitraClip device, follow-up data after the date of the procedure will be excluded from analysis.

7.2 Primary Endpoints

7.2.1 Primary Safety Endpoint

A composite of Single Leaflet Device Attachment (SLDA), device embolizations, endocarditis requiring surgery, Echocardiography Core Laboratory confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery will be the primary measure of safety. The analysis of the primary safety endpoint is a comparison of the freedom from the composite of Device related safety events in the Device group at 12 months to a pre-specified performance goal of 88%.

Hypothesis:

The null and alternative hypotheses are stated as:

$$H_0: P_D(12) \leq 88\% \text{ vs.}$$

$$H_1: P_D(12) > 88\%$$

where $P_D(12)$ is freedom from the primary safety composite in the Device group at 12 months. A one-sided Z-test will be performed to test the null hypothesis against the alternative hypothesis. Kaplan-Meier survival estimate at 12 months, together with the variance estimated using the Greenwood formula, will be used to calculate the Z-statistic. The null hypothesis will be rejected at the 5% significance level if the Z-statistic is greater than 1.645.

Analysis:

Since the primary safety endpoint will be evaluated at 12 months, all data will be truncated at 12 months for the analysis. The Kaplan Meier survival estimate, together with variance estimated by the Greenwood method¹⁷ will be used to set up the test of the null hypothesis as a Z-test. The null hypothesis will be rejected at the 5% level of significance if the test statistic is greater than 1.645.

The primary analysis will be performed in all Device group subjects in whom a MitraClip procedure is attempted. Additional analyses, including sensitivity analyses, are detailed in the **Statistical Analysis Plan**.

7.2.2 Primary Effectiveness Endpoint

Treatment with the MitraClip device is expected to reduce the risk of recurrent HF hospitalization. Recurrent HF hospitalization is the primary effectiveness endpoint for the trial.

Hypothesis:

The null and alternative hypotheses are stated as:

$$H_0: RRR \leq 0 \text{ vs.}$$

$$H_1: RRR > 0$$

where RRR is the relative risk reduction in the rate of recurrent HF hospitalization due to treatment with the MitraClip device. Hospitalizations that are adjudicated by the CEC as

¹⁷ Lee, Elisa T. (2003) Statistical Methods for Survival Data Analysis – 3rd Edition (Wiley Series in Probability and Statistics).

related to heart failure using the pre-specified Clinical Investigational Plan definition will be included as events in the analysis.

Analysis:

The primary analysis will be an ITT analysis. The Joint Frailty Model method will be used to model the recurrent heart failure hospitalization data and estimate the RRR.

The primary effectiveness endpoint will be analyzed when the last subject completes 12 months of follow-up. All available follow-up through 24 months at the time of data cut-off will be included in the analysis. Subjects who do not experience any HF hospitalizations will be censored on their data cut-off date. Subjects who die will be censored on the date of death. Subjects who withdraw from the trial will be censored on the date of withdrawal.

The null hypothesis is rejected if the regression coefficient for the Device group is significant at the 5% level of significance. Beneficial treatment effect is established if the lower one-sided 95% confidence limit of the relative risk reduction is greater than zero.

A sensitivity analysis will be performed, in which this endpoint will be analyzed to include Unplanned Heart Failure visits in addition to heart failure hospitalizations (see definition of Unplanned Heart Failure visits in **APPENDIX A: Definitions**). Additional sensitivity analyses are detailed in the **Statistical Analysis Plan**.

7.3 Secondary Safety Endpoints

The following two secondary endpoints will be used as secondary measures of safety. Power analysis of the secondary safety endpoints are detailed in the **Statistical Analysis Plan**.

7.3.1 Composite 30-Day Secondary Safety Endpoint

A composite of all-cause death, stroke, MI, or non-elective cardiovascular surgery for device related complications in the Device group at 30 days will be used as a secondary measure of safety. The analysis of this secondary safety endpoint is a one-group test against an objective performance goal for the proportion of subjects in the Device group free from the composite of secondary safety events at 30 days.

Hypothesis:

The null and alternative hypotheses may be stated as:

$$\mathbf{H_0: P_D(30) \leq 0.80 \text{ vs.}}$$

$$\mathbf{H_1: P_D(30) > 0.80}$$

where $P_D(30)$ is the proportion of subjects in the Device group free from the composite of secondary safety events at 30 days post procedure. A performance goal of 80% is set under a

conservative assumption that the event rate of the composite is obtained additively from the individual components.

Analysis:

The primary analysis will be performed in all Device group subjects who undergo the MitraClip procedure. An exact test for a single proportion will be performed at the 5% level of significance.

7.3.2 All-Cause Mortality at 12 Months

The relative risk of all-cause mortality at 12 months between the Device and Control groups is a secondary measure of safety.

Hypothesis:

The null and alternative hypotheses are stated as:

$$H_0: RR \geq 1.5 \text{ vs.}$$

$$H_1: RR < 1.5$$

where RR is the relative risk of all-cause mortality at 12 months between the Device and Control groups.

Analysis:

The primary analysis will be an ITT analysis. Follow-up will be truncated at 12 months. A Cox regression model will be used to estimate RR using the hazard ratio. The null hypothesis will be rejected at the 5% significance level if the 95% upper confidence bound for RR is less than 1.5.

7.4 Secondary Effectiveness Endpoints

The following secondary endpoints will be used as secondary measures of effectiveness between the Device group and the Control group. Details of the analyses for the secondary effectiveness endpoints can be found in the **Statistical Analysis Plan**.

7.4.1 MR Severity at 12 Months

Subjects in the Device group are expected to experience greater reduction in MR severity than subjects in the Control group.

Hypothesis:

The null and alternative hypotheses are stated as:

H₀: Categorization of MR severity at 12 months is independent of treatment vs.

H₁: Categorization of MR severity at 12 months is not independent of treatment

7.4.2 Change in Six-Minute Walk Test Distance (6MWD) at 12 Months over Baseline

Improvement in the 6MWD at 12 months from baseline is an important secondary effectiveness endpoint in the comparison of the Device group to the Control group. See **Section 10.14 Measures Taken to Avoid and Minimize Bias During Study Conduct** for measures taken to minimize bias in assessment of the 6MWD. If a subject does not complete a 6MWT, the reason for not completing the test will be documented.

Hypothesis:

The null and alternative hypotheses are stated as:

H₀: $\mu_{T, \Delta 6MWD} - \mu_{C, \Delta 6MWD} \leq 0$ vs.

H₁: $\mu_{T, \Delta 6MWD} - \mu_{C, \Delta 6MWD} > 0$

where $\mu_{T, \Delta 6MWD}$ and $\mu_{C, \Delta 6MWD}$ represent the mean change in distance walked between 12 months and baseline in the Device and Control groups respectively. This endpoint will be evaluated at the 5% level of significance. In addition to a significant p-value for this analysis, the point estimate of the difference in mean improvement between the two groups (Device – Control) should be at least 24 meters to meet this endpoint.

7.4.3 Change in Quality of Life (Kansas City Cardiomyopathy Questionnaire, KCCQ) at 12 Months over Baseline

Improvement in quality of life as measured by the KCCQ Test at 12 months from baseline will be a secondary effectiveness endpoint in the comparison of the Device group to the Control group. See **Section 10.14 Measures Taken to Avoid and Minimize Bias During Study Conduct** for measures taken to minimize bias in assessment of quality of life. If a subject does not complete the KCCQ, the reason for not completing the test will be documented.

Hypothesis:

The null and alternative hypotheses are stated as:

H₀: $\mu_{D, \Delta KCCQ} - \mu_{C, \Delta KCCQ} \leq 0$ vs.

$$H_1: \mu_{D, \Delta KCCQ} - \mu_{C, \Delta KCCQ} > 0$$

where $\mu_{D, \Delta KCCQ}$ and $\mu_{C, \Delta KCCQ}$ represent the mean change in quality of life score between 12 months and baseline in the Device and Control groups respectively. This endpoint will be evaluated at the 5% level of significance. In addition to a significant p-value for this analysis, the point estimate of the difference in mean improvement between the two groups (Device – Control) should be at least 5 units to meet this endpoint.

7.4.4 Change in LVEDV at 12 Months over Baseline

Reduction in MR severity with the MitraClip device is expected to be associated with reduction in LVEDV.

Hypothesis:

The null and alternative hypotheses are stated as:

$$H_0: \mu_{D, \Delta LVEDV} - \mu_{C, \Delta LVEDV} \geq 0 \text{ vs.}$$

$$H_1: \mu_{D, \Delta LVEDV} - \mu_{C, \Delta LVEDV} < 0$$

where $\mu_{D, \Delta LVEDV}$ and $\mu_{C, \Delta LVEDV}$ represent the mean change in left ventricular end diastolic volumes at 12 months over baseline in the Device and Control groups, respectively.

7.4.5 NYHA Functional Class at 12 Months

Reduction in MR severity with the MitraClip device is expected to be associated with improvement in NYHA Functional Class. NYHA Functional Class at 12 months will be compared between the Device and Control groups.

Hypothesis:

The null and alternative hypotheses may be stated as:

$$H_0: P_{D, NYHA I/II} - P_{C, NYHA I/II} \leq 0 \text{ vs.}$$

$$H_1: P_{D, NYHA I/II} - P_{C, NYHA I/II} > 0$$

where $P_{D, NYHA I/II}$ and $P_{C, NYHA I/II}$ represent the proportion of alive subjects with NYHA Class I/II at 12 months in the Device and Control groups, respectively.

7.4.6 Finkelstein-Schoenfeld Analysis of All-Cause Death and Recurrent HF Hospitalization

A hierarchical composite of all-cause death and recurrent HF hospitalization will be analyzed using the Finkelstein-Schoenfeld¹⁸ method.

Hypothesis:

The null and alternative hypotheses are stated as:

$$\mathbf{H_0: } \lambda_{D,Death} = \lambda_{C,Death} \text{ AND } \lambda_{D,Hosp} = \lambda_{C,Hosp}$$

$$\mathbf{H_1: } \lambda_{D,Death} \neq \lambda_{C,Death} \text{ OR } \lambda_{D,Hosp} \neq \lambda_{C,Hosp}$$

Where $\lambda_{D,Death}$ and $\lambda_{C,Death}$ represent the rate of all-cause mortality in the Device group and Control group, respectively. $\lambda_{D,Hosp}$ and $\lambda_{C,Hosp}$ represent the rate of recurrent HF hospitalizations in the Device group and Control group, respectively.

This endpoint will be analyzed when the last subject completes 12 months of follow-up. All available follow-up through 24 months at the time of data cut-off will be included in the analysis. The composite endpoint will be analyzed at the 5% level of significance using the method of Finkelstein and Schoenfeld with death higher in the hierarchy than recurrent HF hospitalizations.

7.4.7 Recurrent Hospitalization - All-Cause

Treatment with the MitraClip device may reduce the risk of recurrent all-cause hospitalization.

Hypothesis:

The null and alternative hypotheses are stated as:

$$\mathbf{H_0: } RRR \leq 0 \text{ vs.}$$

$$\mathbf{H_1: } RRR > 0$$

where RRR is the relative risk reduction in the rate of recurrent hospitalization due to treatment with the MitraClip device. All hospitalizations will be included as events in the analysis.

¹⁸ D. M. Finkelstein and D. A. Schoenfeld, Combining Mortality and Longitudinal Measures in Clinical Trials, *Statistics in Medicine* 1999;18:1341-54..

Analysis:

This endpoint will be analyzed when the last subject completes 12 months of follow-up. All available follow-up through 24 months at the time of data cut-off will be included in the analysis. Subjects who do not experience any hospitalizations will be censored on their data cut-off date. Subjects who die will be censored on the date of death. Subjects who withdraw from the trial will be censored on the date of withdrawal.

7.5 Adjustment for Multiple Testing

Both the primary safety and primary effectiveness endpoints must be met for study success. The secondary endpoints will be evaluated for labeling claims if both primary endpoints are met. Secondary endpoints will be tested sequentially as detailed in the **Statistical Analysis Plan**. Secondary endpoints include the following:

- Composite 30-Day Secondary Safety Endpoint
- All-Cause Mortality at 12 Months
- MR Severity
- Change in 6MWD
- Change in KCCQ QoL score
- Change in Left Ventricular End Diastolic Volume
- NYHA Functional Class
- Hierarchical composite of mortality and recurrent HF hospitalization
- Recurrent hospitalizations, all-cause

7.6 Additional Endpoints

Additional descriptive endpoints will also be reported as described below.

7.6.1 Device or Procedure-Related Adverse Events

Device or procedure-related adverse events are defined as adverse events that are adjudicated by the Clinical Events Committee as possibly, probably or definitely device and/or procedure-related, regardless of the temporal relationship to the MitraClip procedure. Device or procedure-related adverse events will be broken down into those that occur within 30 days of the procedure and those that occur after 30 days of the procedure. Examples of device-related adverse events are:

- myocardial perforation
- Single Leaflet Device Attachment
- embolization of the MitraClip device or MitraClip System components
- iatrogenic atrial septal defect
- mitral valve stenosis
- need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device

7.6.2 Device and Procedure-Related Endpoints

The following device and procedure-related acute endpoints will be reported for the Device group:

- **Implant Rate:** defined as the rate of successful delivery and deployment of the MitraClip device with echocardiographic evidence of leaflet approximation 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 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 duration:** defined as the duration of exposure to fluoroscopy during the MitraClip procedure.

7.6.3 Echocardiographic Endpoints

The following echocardiographic endpoints will be reported for the Device and Control groups at baseline, discharge (or 30 days if discharge echocardiogram is not available), 6 months, 12 months, 24 months and then yearly through 5 years. For continuous variables, change from baseline to each follow-up will also be reported:

- MR Severity Grade

- Effective Regurgitant Orifice Area
- Regurgitant Volume
- Regurgitant Fraction
- Left Ventricle 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
- Mean Mitral Valve Gradient
- Systolic Anterior Motion of the mitral valve (present or absent)
- Cardiac Output
- Forward Stroke Volume

7.6.4 Clinical Endpoints

The following clinical endpoints will be reported for the Device and Control groups:

- Kaplan-Meier freedom from the components of the primary safety composite at 12 months, and yearly through 5 years (Device group only)
- Kaplan-Meier freedom from the primary safety composite at 24 months and yearly through 5 years (Device group only)
- Kaplan-Meier freedom from all-cause mortality at 12 months, 24 months and yearly through 5 years
- Kaplan-Meier freedom from: (1) cardiovascular mortality (2) the first HF related hospitalization (3) the first cardiovascular hospitalization (4) the first HF related hospitalization or all-cause mortality at 12 months and 24 months and then yearly through 5 years

- NYHA Functional Class at baseline, 30 days, 6 months, 12 months, 24 months and then yearly through 5 years
- 6MWD at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up)
- KCCQ QoL scores at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up)
- SF-36 QoL scores at baseline, 30 days, 6 months, 12 months and 24 months (and change from baseline to follow-up)
- Mitral valve surgery (including type of surgery), new use of CRT, new use of single or dual chamber pacemaker, permanent LVAD implant, heart transplant, additional MitraClip device intervention in Device group or *de novo* MitraClip device intervention in Control group, including reason for intervention through 5 years
- Responder analysis for 6MWD, where responder is defined as alive and experiencing an improvement of 24 meters and 50 meters at 12 months (difference in proportion of responders between Device and Control groups) at 12 months and 24 months
- Responder analysis for LVEDV Index, where responder is defined as alive and experiencing an improvement of 12 ml/m² (difference in proportion of responders between Device and Control groups) at 12 months, 24 months and then yearly through 5 years
- Responder analysis for QoL (KCCQ), where responder is defined as alive and experiencing an improvement of 5 points (difference in proportion of responders between Device and Control groups) at 12 months and 24 months
- Each subscale for QoL (KCCQ) (difference in means between Device and Control groups) at 12 months and 24 months
- Length of index hospitalization for MitraClip procedure (Device group)
- Number of hospitalizations and reason for hospitalization (i.e. heart failure, cardiovascular, non-cardiovascular) at 12 months and 24 months in each of the Device and Control groups
- Number of days alive and out of hospital from the time of randomization (difference in medians between Device and Control groups) to 12 months, 24 months and then yearly through 5 years
- Number of days hospitalized from the “Treatment” visit (difference in medians between Device and Control groups) at 12 months, 24 months and then yearly through 5 years

- Proportion of alive time in hospital will be summarized and compared between Device and Control groups at 12 months, 24 months and then yearly through 5 years
- Proportion of subjects living in the baseline location at 12 months, 24 months and then yearly through 5 years
- Mitral valve replacement rates will be summarized and compared between Device and Control groups at 12 months, 24 months and then yearly through 5 years
- New onset of permanent atrial fibrillation at 12 months, 24 months and then yearly through 5 years
- Mitral stenosis at 12 months, 24 months and then yearly through 5 years
- Clinically significant atrial septal defect (ASD) that requires intervention at 12 months, 24 months and then yearly through 5 years
- Device-related complications in Device group subjects and Control group subjects who the undergo MitraClip procedure through 5 years
- BNP or NT-proBNP levels at baseline, 30 days and 12 months
- Modified Rankin Scale Score at baseline, 30 days, 6 months, 12 months
- Major bleeding at 30 days
- Prolonged ventilation at 30 days
- Average dosages of GDMT at baseline, 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years
- The number and reasons for (1) any changes in GDMT and GDMT dosage from baseline at 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years and (2) any changes in GDMT from baseline that result in a larger than 100% increase or 50% decrease in dose at 30 days, 6 months, 12 months, 24 months, and then yearly through 5 years
- Peak VO₂ from cardiopulmonary exercise testing (CPX) in the subset of patients participating in the CPX sub-study at baseline and 12 months

7.7 Power and Sample Size

A total sample size of approximately 610 randomized subjects is planned. The power for the primary safety endpoint when approximately 305 Device group subjects complete 12 months of follow-up is >95%. The power for the primary effectiveness endpoint with follow-up through 24 months in approximately 610 subjects when the last subject completes 12 months

of follow-up is ~80%. The overall power for the study for the primary endpoints with the planned randomization of approximately 610 subjects is ~80%. Details of sample size and power calculations are included in the **Statistical Analysis Plan**.

7.8 Trial Success

The trial will be considered successful if the primary safety and primary effectiveness endpoints are met. Additional labeling claims may be made based on the secondary endpoints.

8 Adverse Events

8.1 Definition of Adverse Event and Serious Adverse Event

8.1.1 Adverse Event (AE)

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

This definition includes events related to the investigational medical device or comparator and/or the procedures involved. For users or other persons, this definition is restricted to events related to the investigational medical device.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Device failure may constitute an adverse event if an undesirable experience occurs

Adverse events information will be collected throughout the trial. Adverse events will be recorded on the electronic case report forms by the Investigator or designee. Event description, date of onset, severity, duration, and relationship to device will be recorded on the appropriate electronic case report form. Adverse events will be monitored through the course of the trial. A list of adverse events, which may result from this procedure, is located below in **Table 3**.

Note: Unchanged, chronic conditions are not adverse events and should not be recorded on the eCRF Adverse Event form. Pre-existing conditions that have not worsened are not considered AEs.

8.1.2 Serious Adverse Event

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

- a) Led to a death,
- b) Led to a serious deterioration in health that either:
 - 1) Resulted in a life-threatening illness or injury, or
 - 2) Resulted in a permanent impairment of a body structure or a body function, or
 - 3) Required in-patient hospitalization or prolongation of existing hospitalization, or
 - 4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.
- d) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

8.1.3 Anticipated Adverse Events

Table 3 lists the following anticipated events that have been identified as possible complications from the MitraClip procedure expected in this trial. Please also refer to the list of anticipated events in the MitraClip System Instructions for Use (IFU) and package insert for other (drug or device) therapies required per protocol.

Table 3: Anticipated Adverse Events (MitraClip Procedure)

| | |
|--|---|
| Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex) | Hypotension/hypertension |
| Aneurysm or pseudo-aneurysm | Infection |
| Arrhythmias | Injury to mitral valve complicating or preventing later surgical repair |
| Atrial fibrillation | Lymphatic complications |
| Atrial septal defect requiring intervention | Mesenteric ischemia |
| Arterio-venous fistula | MitraClip erosion, migration or malposition |
| Bleeding | MitraClip Device thrombosis |
| Cardiac arrest | MitraClip System component(s) embolization |
| Cardiac perforation | Mitral stenosis |
| Cardiac tamponade/Pericardial Effusion | Mitral valve injury |
| 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 Device) | Septicemia |
| | Shock, Anaphylactic or Cardiogenic |
| Emergency cardiac surgery | Single leaflet device attachment (SLDA) |
| Endocarditis | Skin injury or tissue changes due to exposure to ionizing radiation |
| Esophageal irritation | Stroke* or transient ischemic attack (TIA) |
| Esophageal perforation or stricture | Urinary tract infection |
| Failure to deliver MitraClip to the intended site | Vascular trauma, dissection or occlusion |
| Failure to retrieve MitraClip System components | Vessel spasm |
| Fever or hyperthermia | Vessel perforation or laceration |
| Gastrointestinal bleeding or infarct | Worsening heart failure |
| Hematoma | Worsening mitral regurgitation |
| Hemolysis | Wound dehiscence |
| Hemorrhage requiring transfusion | |

*Subjects must have a visit with a neurologist and mRS assessment 90 days after onset of stroke

8.1.4 Unanticipated Adverse Device Effect

Unanticipated adverse device effect (UADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the MitraClip system, if that effect, problem, or death was **not previously identified in nature, severity, or degree of incidence** in the Clinical Investigational Plan, including the Device Instructions for Use, or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.2 Device Deficiency/Product Experience

Device deficiency (DD) 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

Product Experience (PE) is defined as any expression of customer concern or dissatisfaction, including adverse events and patient issues that occurred during or after the use of a commercially available medical device.

8.3 Device or Procedure-Relationship

Determination of whether there is a reasonable possibility that the MitraClip device or MitraClip procedure caused or contributed to an AE is to be assessed by the Investigator and recorded on the appropriate eCRF form as not related, possibly related, probably related, definitely related or unknown. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and/or presence (or absence) of a more-likely cause.

Definitions for determination of MitraClip device relationship include:

Not Related: Exposure to the MitraClip device has not occurred (no temporal relationship), or the occurrence of the adverse event is not reasonably related in time, or there is a definite alternative etiology, or it is biologically implausible for the adverse event to be related to the use of the device.

Possibly Related: Exposure to the MitraClip device has occurred; and it cannot be ruled out that the device is not responsible for the adverse event.

Probably Related: Exposure to the MitraClip device has occurred or the adverse event is reasonably related in time; and the device is more likely than other alternative causes to be responsible for the adverse event.

Definitely Related: Exposure to the MitraClip device has occurred or the adverse event is related in time; and the device is definitely responsible for the adverse event.

Unknown Exposure to the device and the occurrence of adverse event cannot be reasonably determined to be unrelated to the device. If the relationship is identified as unknown it will be treated as related to the device.

Determination of MitraClip procedure relationship includes assessment of AEs for relationship to any of the following: discontinuation of medications for the MitraClip procedure, administration of local or general anesthesia, or the MitraClip procedure. Relationship of MitraClip procedure will be assessed regardless of the temporal relationship to the MitraClip procedure.

8.4 Adverse Event/Device Deficiency/Product Experience Reporting

8.4.1 Adverse Event Monitoring

The Investigator will monitor the occurrence of adverse events for each subject during the course of the trial. All adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records will be documented on the eCRF Adverse Event form. A fax form will be made available to allow the investigator to report SAEs and device deficiencies in the event the eCRF is not available.

For all registered subjects, AEs (any new event/experience that was not present at baseline or worsening of an event present at baseline) will be collected. Adverse events will be monitored through the course of the trial. Additional information related to a previously reported adverse event should be updated within the appropriate electronic case report form. The SAE and device deficiency should be entered in the eCRF as soon as the system is available.

Unchanged, chronic non-worsening or pre-existing conditions are not adverse events and should not be recorded in the eCRF.

8.4.2 Serious Adverse Event Reporting to Sponsor and IRB/EC

The Investigator will monitor the occurrence of AEs for each subject during the course of the clinical trial/investigation and report as required by this protocol in section 8 per AE and SAE definitions. AEs need to be collected from the time of randomization for randomized subjects and from the initiation of the MitraClip procedure for roll-in subjects on the appropriate AE eCRF form. Additional information with regards to an AE should be updated within the AE eCRF.

A fax form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the eCRF system. This does not replace the eCRF reporting system. All information must still be entered in the eCRF system as soon as feasible.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than 3 calendar days from the day study personnel became 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 that the event met the criteria of a serious adverse event must be recorded in the source document.

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the eCRF system, however need to be reported on the SAE Notification Form provided by Sponsor.

The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

8.4.3 Unanticipated Adverse Device Effect (UADE) Reporting to Sponsor and IRB/EC

The Investigator should report any UADE to the sponsor and the IRB/EC within 3 calendar days following the investigator's knowledge of the event. The sponsor is required to report the findings of the investigation of any UADE to the FDA, other appropriate regulatory agency and the IRB/EC as soon as possible, but in no event later than 10 working days after knowledge of the event.

8.4.4 Unanticipated Serious Adverse Device Effect (USADE) Reporting to Sponsor and IRB/EC

Abbott Vascular requires the Investigator to report any unanticipated serious adverse device effect (USADE) to the sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements. The sponsor is required to report the findings of the investigation of any USADE to regulatory agencies and the IRB/EC per local requirements.

8.4.5 Device Deficiency/Product Experience Reporting

The investigator should report all Device Deficiencies/Product Experiences to the Sponsor as soon as possible but no later 3 calendar days from the day the study personnel becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The device, if not implanted or not remained in the subject, should be returned to Abbott Vascular.

Device deficiencies should be reported to the IRB/EC per the investigative site's local requirements.

8.4.6 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report the SAEs and DDs/PEs to the country regulatory authority, per local requirements.

8.5 Anticipated Adverse Event Rates

To comply with ISO 14155:2011 requirement to provide the likely incidence of foreseeable adverse events, **APPENDIX F: Rates of Foreseeable Adverse Events** has been included.

8.6 Adjudication of Events

The Sponsor will review all adverse events. Adverse events requiring adjudication will be submitted to the Clinical Events Committee (CEC). Refer to **Section 10.4 Clinical Events Committee** for the CEC's role and responsibility.

9 Direct Access to Source Data/Documents

The Investigator/institution will permit and assure direct access to source data/documents (e.g., hospital/clinic/office charts, catheterization reports, laboratory results, etc.) for trial-related monitoring, audits, IRB/EC review, and regulatory inspections.

Subjects providing informed consent agree to allow the Sponsor representatives or designee access and copying rights to pertinent information in their medical records relevant to trial participation.

The Investigator will obtain, as part of the informed consent, permission for Sponsor monitors and designees, including auditors, or regulatory authorities to review, in confidence, any records identifying the subjects in this clinical trial/investigation. This information may be shared with regulatory agencies; however, per relevant confidentiality and privacy rules (HIPAA), the Sponsor and its designees will not otherwise release the subject's personal, private and protected health information.

10 Quality Control and Quality Assurance

To ensure uniformity of subject assessment across all study sites, regulatory compliance by both Sponsor and investigational sites, and that the trial is conducted in accordance with the Clinical Investigational Plan, proper quality control and assurance procedures will be

followed in this trial. These controls include establishment of study committees, training, monitoring and support of quality audits.

10.1 Steering Committee

The Steering Committee is an expert advisory leadership group that provides scientific and medical input on trial design, data collection, data analyses and interpretation of results. It is intended that the Steering Committee leverage the experiences, expertise, and insights of key individuals at organizations committed to cardiovascular excellence, and provide an organizational structure within which to ensure scientific objectives of the trial are adequately addressed. The Steering Committee is charged with driving commitment to the trial, motivating investigational sites, encouraging patient recruitment, and producing high quality data.

10.2 Central Eligibility Committee

An independent Eligibility Committee will confirm that each subject is on optimal therapy including GDMT prior to being considered for the trial. The committee will also confirm through discussion with the site investigators (including the site surgeon) that the patient is not appropriate for mitral valve surgery, even if randomized to the Control group. The committee will also categorize whether or not the subject is extremely high surgical risk, as defined in **APPENDIX A: Definitions**).

The Eligibility Committee will be comprised of, at a minimum, representatives from the following specialties: CT surgery (with expertise in mitral valve surgery) and cardiology (with expertise in heart failure). The composition, guiding policies, and operating procedures governing the Eligibility Committee are described in a separate **Eligibility Committee Manual of Operations**.

10.3 Central Echocardiography Core Laboratory (ECL)

The ECL will be responsible for reviewing subject's screening echocardiography images to determine if the subject meets the MR severity eligibility criterion prior to the subject being considered eligible for the trial.

MR severity and left ventricular measurements, along with other measures, will be assessed by the ECL at baseline and follow-up.

The ECL will operate according to a separate **ECL Manual of Operations**.

10.4 Clinical Events Committee

The Clinical Events Committee (CEC) is a multi-disciplinary team comprised of qualified physicians who are not investigators in the trial. The composition, guiding policies, and

operating procedures governing the CEC are described in a separate **CEC Manual of Operations**. The CEC will review and adjudicate pre-specified events reported by trial investigators or identified by the Safety & Surveillance personnel/designate for the trial as documented in CEC Manual of Operations (MOPs). Every effort will be made to blind the CEC to the subject's treatment assignment.

10.5 Data Monitoring Committee

The Data Monitoring Committee (DMC) will monitor the safety of subjects throughout trial registration on an on-going basis. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC charter.

The Data Monitoring Committee (DMC) will serve in an advisory role to Abbott Vascular to ensure safety by reviewing cumulative data from the clinical trial at pre-scribed intervals for the purpose of safeguarding the interests of trial participants. The DMC will meet periodically at a frequency set out in the DMC charter to monitor the safety of subjects registered in the study. The DMC may consider a recommendation for modifications or termination of the study based on safety concerns. The recommendations of the DMC are not binding, and all final decisions regarding the clinical investigation, however, rest with Abbott Vascular and the Steering Committee.

10.6 Publication Committee

The Publication Committee will oversee and guide the ongoing scientific presentation and publication activities for the COAPT Trial. The Publication Committee will determine policies and strategies regarding presentations and/or publications arising from study generated data. The committee will also review and approve all external requests for accessing study-related data and strategies for presentation and publication. The Committee will follow Abbott Vascular applicable policies and standard operating procedures. The Steering Committee Chairs will chair the COAPT Publication Committee. The composition, guiding policies, and operating procedures governing the Publication Committee are described in detail in a separate Publication Committee Charter.

10.7 Training

10.7.1 Site Training

All Investigators and site clinical trial 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 or clinical trial personnel will include, but is not limited to, device training, the Clinical Investigational Plan requirements, investigational device usage, electronic case report form completion, trial personnel responsibilities and regulatory requirements.

All Investigators or clinical trial personnel that are trained must sign a training log upon completion of the training. Investigator or clinical trial personnel must not perform any trial-related activities prior to signing the training log unless these activities are standard of care at the site. Prior to the start of the clinical trial, the trial monitor or designee will visit each site where the clinical trial will be conducted. The clinical trial monitor will ensure that sites' clinical trial personnel are informed about and understand the clinical trial requirements.

The following matrix describes the training requirements for study personnel at each site. Training will be provided by Abbott Vascular:

| MITRACLIP PROCEDURE ROLE | Procedural Role | | |
|--------------------------|---------------------|----------------|-----------------------|
| | Implanter Curricula | Echo Curricula | System Prep Curricula |
| Implanter | ✓ | | |
| Echo | | ✓ | |
| System preparation | | | ✓ |

✓ = required

| STUDY ROLE | Clinical Investigational Plan Elements | | | | | | | | |
|-------------------------------------|--|--------------------------|----------------------|--------------------|-----|-----------------------|-------|--------------------|--|
| | Study Design | Informed Consent Process | Eligibility Criteria | 6-Minute Walk Test | QOL | NYHA Functional Class | eCRFs | AE / SAE Reporting | modified Rankin Scale Certification ^a |
| Site Principal/Primary Investigator | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Site Sub-Investigator | ✓ | ✓ | ✓ | | | ✓ | | ✓ | |
| Study Coordinator #1 (non-blinded) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Study Coordinator #2 (blinded) | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ |

✓ = required

a = certification to be verified by Abbott Vascular

10.7.2 Training of Sponsor's Monitors

Sponsor's designated monitors will be trained to the Clinical Investigational Plan, case report forms and investigational device usage (as appropriate), according to the Sponsor's written procedures.

10.7.3 Training of Sponsor's Designees or Vendors

All Sponsor partners and/or designated vendors (e.g., Echocardiography Core Laboratory) responsible for any function in the conduct of the clinical trial will be trained to the Clinical Investigational Plan and other trial documents (as appropriate).

10.8 Monitoring

Sponsor and/or designee will monitor the study over its duration according to the pre-specified monitoring plan and relevant standard operating procedures which will include the planned extent of source data verification.

10.8.1 Designated Monitors

Study monitors are individuals who are designated to oversee the progress of a study. These individuals are appropriately trained and qualified to monitor the progress of a clinical trial. The study Sponsor may designate additional monitors at any time during the study. The Sponsor should be contacted for information on the person(s) responsible for monitoring activities at the following address:

Abbott Vascular Inc.
3200 Lakeside Drive
Santa Clara, CA 95054

10.8.2 Monitoring Visits

Scheduled visits to the clinical investigational site may occur at the following times: prior to the start of the clinical study (pre-study qualification visit), at initiation of the study (at first implant or shortly thereafter), interim visits throughout the clinical study as required, annually, and upon completion of the clinical study.

10.8.2.1 Pre-study Qualification Visit

A pre-study visit may be conducted by Sponsor personnel (or designees) to review the Clinical Investigational Plan and regulatory requirements with the investigator and the trial personnel to assure that they:

- Understand the requirements for an adequate and well-controlled clinical trial.
- Understand and accept the obligation to conduct the clinical investigation in accordance with the local, state and national (federal) regulations.
- Understand the investigational status of the device and the requirements for its use and accountability.
- Understand and accept the obligation to obtain informed consent in accordance with the local, state and national (federal) regulations.
- Understand and accept the obligation to obtain IRB/EC approval before the clinical study is initiated, ensure continuing review of the study by the IRB/EC, and keep the Sponsor informed of IRB/EC approval and actions concerning the clinical trial.
- Have access to an adequate number of eligible subjects to participate in the trial (at least 1 per month).
- Have adequate facilities and resources to conduct the trial. This includes resources appropriate for use of electronic data capture (EDC) systems.
- Have sufficient time from other obligations to carry out the responsibilities of the clinical trial.

10.8.2.2 Initiation Visit

Sponsor clinical personnel (or designees) may provide assistance for both scientific concerns and study management issues during the initiation visit. Any observations will be documented and issues requiring follow-up will be identified on a monitoring report.

10.8.2.3 On-Site Interim Monitoring Visits

On-site monitoring visits will occur on an as-required basis (and at least annually) to assess adherence to the clinical investigation plan, IRB/EC review of study progress, maintenance of records and reports, and selected review of source documents for accuracy, completeness, legibility, and omissions. The monitors will acquire information to assess the progress of the study (toward meeting study objectives) and identify any concerns that stem from observation of device performance and/or review of the investigator's subject records, study

management documents, and subject informed consent documents. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on eCRFs and device information. Monitoring reports will be generated along with communications to the investigator, which document the result of the monitoring visits and any recommended actions. Resolution of concerns and completion of assigned tasks will be documented.

The Institution must provide documentation of Echo machine calibration and/or maintenance records to the Sponsor on a routine basis. Abbott Vascular and/or designee will periodically monitor the calibration documentation, to ensure the machine is properly functioning for the duration of the study.

10.8.2.4 Final Monitoring Review

Depending upon the status of the study at each center, a close-out or final visit may be conducted. Any ongoing responsibilities will be discussed with the investigator and the study center coordinator. A final monitoring report, which includes, at a minimum, disposition of any unused devices, will be completed.

10.9 Quality Assurance Audit

The Sponsor may conduct periodic Quality Assurance audits (on-site audits) at various clinical trial sites. A sponsor representative or designee may request access to all trial records, including source documentation, for inspection and duplication during a Quality Assurance audit. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the audit process.

10.10 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the Clinical Investigational Plan, except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject or eliminate an apparent immediate hazard to the subject. All deviations must be reported to the Sponsor. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the Clinical Investigational Plan and regulatory requirements and dealt with according to written procedures.

10.10.1 Deviations with Expedited Reporting Requirements

For the following types of protocol deviations (per 21 CFR 812.150), an investigator is required to notify the Sponsor and the IRB/EC within 5 business days of the deviation.

- Emergency Deviation from the Clinical Investigational Plan (a deviation to protect the life or physical well-being of a subject in an emergency).
- Failure to obtain Informed Consent.

Notification to the Sponsor and/or the IRB/EC should be documented and maintained in the clinical study file at the site and at Abbott Vascular.

10.10.2 Non-Critical Deviations

Protocol deviations which do not have the urgency associated with expedited notification or prior Abbott Vascular/ IRB/EC approval (as discussed in the above paragraphs) will be reported upon discovery, such as during completion of eCRFs or a monitoring visit.

10.11 Device Malfunction

Device malfunction is the failure of the MitraClip device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of the MitraClip device refers to the intended use for which the device is labeled or marketed. An occurrence of any device malfunction during the MitraClip placement procedure should be reported to the Sponsor as soon as possible. The device, if not implanted in the subject, should be returned to Abbott Vascular. If a device malfunction is observed during the follow-up period via echocardiography images, such failure should be reported to the sponsor as soon as possible. A device malfunction may or may not be related to an adverse event in a subject. If adverse events occurred as a result of the device malfunction, then the adverse events must be reported as well.

10.12 Device Misuse

A misused device (one that is used by the Investigator in a manner that is contradictory to the Instructions for Use) will not be considered a malfunction.

10.13 Sponsor Support to Clinical Trial/Investigation Site for Regulatory Body Inspection

In the event that an Investigator is contacted by a Regulatory Agency regarding this clinical trial/investigation, the Investigator will notify the Sponsor immediately. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical trial/investigation (e.g., Form FDA 483, Inspectional Observations, and warning letters). As necessary, the Sponsor may provide any assistance in responding to regulatory inspections.

10.14 Measures Taken to Avoid and Minimize Bias During Study Conduct

Due to the nature of the treatment in the two randomized groups, the subject, some site personnel and some Sponsor personnel will be aware of treatment assignment. The following steps will be taken to minimize bias in the conduct of the trial and analyses of clinical data.

10.14.1 Subject Recruitment and Randomization

Investigational sites will attempt to recruit consecutive subjects who meet trial eligibility criteria (see **Section 5 Trial Design, Scope and Duration** for more information on the participation of women in the trial).

- Candidates will be considered for the trial after they have been informed of trial requirements and have signed the informed consent form. See **Section 6.4 Subject Screening and Informed Consent** for additional details on subject screening and informed consent process.
- Transthoracic echocardiographic criteria for trial eligibility will be confirmed by an independent Echocardiography Core Laboratory
- All baseline tests and assessments must be completed prior to randomization
- Subjects will be randomized only after the sites' clinical personnel have confirmed and documented that the subject has met all eligibility criteria, the ECL has confirmed the MR severity eligibility criterion, and the Eligibility Committee has confirmed that the subject is on optimal therapy including GDMT and is not appropriate for mitral valve surgery.
- Randomization within each site will be stratified by site and cardiomyopathy etiology (i.e. ischemic or non-ischemic), assigned in permuted block sizes, and block sizes will not be disclosed to the sites.
- A centralized randomization service will be used.

10.14.2 Maintaining Similar Levels of Follow-up

In order to maintain similar levels of contact between the investigational site and subjects, all subjects will have a "Treatment" visit. During the "Treatment" visit for the Control group, subjects will be seen by a HF specialist, and will undergo a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications. Subjects in the Device group will undergo the MitraClip procedure during the "Treatment" visit. The follow-up schedule post-"Treatment" visit is identical for both groups and both groups will be followed by the HF specialist.

10.14.3 Administration of Assessments

Site personnel assessing NYHA Functional Class and administering the 6MWT and QoL questionnaires will not have knowledge of the subject's treatment assignment and will not be involved in day-to-day activities of the COAPT trial. Additionally, personnel performing these assessments will not have access to the eCRFs. A standardized script will be used when administering the assessments and the subject will be reminded to not reveal their treatment history to the administrator. To minimize bias and undue influence, the QoL questionnaires will be completed by the subject, unless the subject is unable to complete the questionnaire on their own (in such cases, a note to file must be completed to document the inability of subject to complete the questionnaire).

10.14.4 Review of Echocardiography Images

MR severity and left ventricular measurements, along with other measures, will be assessed by an Echocardiography Core Lab (ECL) at baseline and follow-up. For follow-up echoes, the ECL will not have knowledge of the follow-up visit.

10.14.5 Safety and Effectiveness Monitoring

- All adverse events will be reviewed by Abbott Vascular.
- Adverse events requiring adjudication will be submitted to an independent Clinical Events Committee (CEC). Every effort will be made to keep the CEC blinded to the subject's treatment assignment.
- A Data Monitoring Committee (DMC) will review accumulating safety and effectiveness data as described in **Section 10.5**.

10.14.6 Follow-Up Compliance

The Sponsor will work with investigational sites to maintain high follow-up compliance. The following are strategies for increasing compliance:

1. During site initiation and training, the Sponsor will emphasize to the site the importance of subject follow-up, and that the site should communicate this importance to each subject.
2. Sites will be informed to promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit.
3. If a scheduled visit is missed due to subject illness, transportation issues, or travel, the site will be advised to:

- a. Reinforce the necessity of follow-up visits;
 - b. Identify alternate transportation sources, and involve the Sponsor if necessary.
4. Sites will be instructed to ask subjects who withdraw during the trial to provide the reason for withdrawal and ask them if the investigator may contact them once more at the end of the trial follow-up.
 5. Follow-up rates will be monitored closely so follow-up problems may be identified and addressed as soon as possible.
 6. For subjects lost-to-follow-up, sites may be requested to examine the Social Security Death Index to determine subject status (only the status will be sent to Sponsor, not any subject identifying information).

In addition to aforementioned steps, investigational sites will be educated on the importance of maintaining low rates of withdrawals in both Device and Control groups, and will be expected to make all effort to maintain low withdrawals during trial conduct. Withdrawals from the trial will require discussion between investigator and the Sponsor.

10.14.7 Analysis

The primary analysis for the effectiveness endpoint will be performed on an intention to treat basis. The primary analysis for the safety endpoint will be performed in Device group subjects who undergo the MitraClip procedure.

10.15 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent required by law. Every attempt will be made to remove patient identifiers from clinical study documents and eCRFs. For this purpose, a unique subject identification code will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be traced back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed, to the extent permitted by law. The identity of a subject will never be disclosed in the event that study data are published.

The Sponsor requires that the study sites comply with the subject confidentiality provisions of the Health Insurance Portability and Accountability Act (HIPAA) issued by the U.S. Department of Health and Human Services (HHS). Sites should maintain patient privacy in accordance to federal regulations (45 CFR Parts 160 and 164), local regulations, and institutional requirements.

11 Data Handling and Record Keeping

Clinical data will be collected pre-randomization during the screening period to establish subject eligibility at baseline, during the MitraClip device placement procedure and throughout the MitraClip placement hospital stay for the Device group, during the “Treatment” visit for the Control group and during the follow-up period for all subjects.

All eCRF data collection will be performed through a secure web portal and all authorized personnel with access to the Electronic Data Capture (EDC) system must use an electronic signature access method to enter, review or correct data. Electronic signature procedures shall comply with the CFR Title 21 Part 11 and the ICH Guidelines for Good Clinical Practice (GCP) (Topic E6, April 2000) Section 5.5.3. Passwords and electronic signatures will be strictly confidential.

The Sponsor’s monitors (or designees) will review all electronic case report forms. The Sponsor’s data management group will perform all data management activities, including data review, database cleaning, and issuing and resolving data queries, and documentation of the systems and procedures to be used.

All eCRF data will be downloaded from the EDC system and reformatted for analysis in a data structure acceptable to Abbott Vascular. The data will be subjected to consistency and validation checks within the EDC system and will be subject to supplemental validation following download.

Completed eCRFs with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the investigator’s site and a backup copy archived with Abbott Vascular.

11.1 Source Documentation

IDE regulations (21 CFR 812) and GCPs require that the Investigator maintain information in the subject’s medical records that corroborates data collected on the eCRFs. Throughout the clinical trial duration, the sites’ investigators will maintain complete and accurate documentation including but not limited to medical records, clinical trial progress records, laboratory reports, electronic case report forms, signed informed consent forms, device accountability records, correspondence with the IRB/EC and clinical trial monitor or sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical trial/investigation. Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the sponsor, reviewing committees, or the core lab, should have all subject identifiers removed and replaced with the subject number. In order to comply with these regulatory requirements/GCP the following information should be included in the subject record at a minimum and if applicable to the investigation:

- Medical history/physical condition of the subject before involvement in the trial sufficient to verify Clinical Investigational Plan entry criteria

- Dated and signed notes on the day of entry into the trial referencing the sponsor, Clinical Investigational Plan 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)
- Adverse events 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 device relationship assessment of SAEs.
- Study required laboratory reports and 12-lead ECGs, signed and dated for review and annotated for clinical significance of out of range results.
- Notes regarding Clinical Investigational Plan-required and prescription medications taken during the trial (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the trial
- Any other data required to substantiate data entered into the CRF

11.2 Electronic Case Report Form Completion

Primary data collection based on source-documents and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the Clinical Investigational Plan and eCRF completion. eCRF data will be collected for all enrolled patients. Sponsor or designee will provide clinical monitoring as specified in **Section 10.8 Monitoring**.

11.3 Site Record Retention

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

12 Ethical Consideration

12.1 Institutional Review Board/Ethics Committee Review

Institutional Review Board (IRB) or Ethics Committee (EC) approval for the Clinical Investigational Plan and informed consent form will be obtained by the Principal Investigator

at each investigational site prior to participation in this clinical trial/investigation. The approval letter must be signed by the IRB/EC chairman or authorized representative prior to the start of this clinical trial and a copy must be provided to the Sponsor. No changes will be made to the Clinical Investigational Plan or informed consent form without appropriate approvals, including IRB/EC, the Sponsor, and/or the regulatory agencies.

Until the clinical trial/investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical trial/investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical trial/investigation, according to each institution's IRB/EC requirements. Further, any amendments to the Clinical Investigational Plan as well as associated informed consent form changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements. Acknowledgement/approval by the IRB/EC of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must also be provided to the Sponsor.

No investigative procedures other than those defined in this Clinical Investigational Plan will be undertaken on the registered subjects without the written agreement of the IRB/EC and the Sponsor.

13 Risk Analysis

Patients with untreated clinically significant functional MR are highly symptomatic, have a high rate of heart failure hospitalizations, poor quality of life and impaired functional capacity. Current options to treat their FMR include medical management and mitral valve repair or replacement surgery.

Medical management of patients with MR is intended to reduce symptoms and improve quality of life; yet medical management does not treat the mechanical malcoaptation of the mitral valve leaflets, and therefore is not a long-term treatment solution for their MR. Mitral valve surgery, on the other hand, is an invasive approach and in functional MR, there is limited evidence that the benefits of mitral valve surgery outweigh the risks. Mitral valve surgery is not recommended as standard of care in the most recent 2013 ACCF/AHA Heart Failure guidelines, in which mitral valve surgery is considered a class IIb recommendation⁶.

In this clinical trial, the overall risk versus benefit analysis of the MitraClip System is based on weighing the potential risks and benefits of the MitraClip System against the risks and benefits associated with no MitraClip intervention.

13.1 Potential Risk

The potential risks associated with the MitraClip procedure can be grouped into two categories. First, there are potential risks associated with standard cardiac catheterization, including transseptal catheterization, the transesophageal echocardiogram (TEE) probe and

the potential risks of general anesthesia. Second, there are potential risks uniquely associated with the use of the MitraClip System.

Risks associated with standard cardiac catheterization, TEE probe and anesthesia include, but are not limited to, the following:

- Death
- Myocardial infarction
- Stroke or transient ischemic attack (TIA)
- Cardiac arrest
- Shock, Anaphylactic or Cardiogenic
- Cardiac perforation
- Cardiac tamponade/Pericardial Effusion
- Hematoma
- Arterio-venous fistula
- Coagulopathy
- Bleeding
- Hemorrhage requiring transfusion
- Infection
- Endocarditis
- Septicemia
- Pain
- Dizziness
- Dyskinesia
- Arrhythmias
- Atrial fibrillation

- Emboli (air or thrombus)
- Vascular trauma, dissection or occlusion
- Peripheral ischemia
- Fever or hyperthermia
- Prolonged angina
- Pulmonary congestion
- Pulmonary thrombo-embolism
- Hypotension/hypertension
- Renal insufficiency or failure
- Allergic reaction(anesthetic, contrast Heparin, nickel alloy, latex)Drug reaction to anti-platelet/anticoagulation agents/contrast media
- Nausea/vomiting
- Prolonged ventilation
- Respiratory failure/atelectasis/pneumonia
- Gastrointestinal bleeding or infarct
- Aneurysm or pseudo-aneurysm
- Deep venous thrombus (DVT)
- Dyspnea
- Edema
- Esophageal irritation
- Esophageal perforation or stricture
- Lymphatic complications
- Multi-system organ failure
- Mesenteric ischemia

- Urinary tract infection
- Vessel spasm
- Vessel perforation or laceration
- Worsening heart failure
- Wound dehiscence
- Skin injury or tissue changes due to exposure to ionizing radiation

Potential risks specifically associated with the use of the MitraClip System include, but are not limited to, the following:

- MitraClip System component(s) embolization
- MitraClip erosion, migration or malposition
- MitraClip Device thrombosis
- Failure to deliver MitraClip to the intended site
- Worsening mitral regurgitation
- Mitral stenosis
- Mitral valve injury
- Failure to retrieve MitraClip System components
- Hemolysis
- Conversion to standard valve surgery
- Atrial septal defect requiring intervention
- Single leaflet device attachment (SLDA)
- Emergency cardiac surgery
- Dislodgement of previously implanted devices
- Chordal entanglement/rupture
- Injury to mitral valve complicating or preventing later surgical repair

13.2 Risk Management Procedures

Risks associated with the use of the MitraClip System are minimized through device design, Investigator selection and training, pre-specified subject eligibility requirements, study monitoring to ensure adherence to the Clinical Investigational Plan and the use of an independent Data Monitoring Committee.

Specifically, the risk management strategy includes the following

- AEs will be recorded per **Section 8: Adverse Events** of this Clinical Investigational Plan and will be reported and monitored throughout the follow-up period.
- The sites will be notified of unexpected adverse device effects and other safety concerns that could negatively impact the safety of the subjects if such issues arise.
- All investigators will be trained on the device, the IFU, and the trial protocol prior to participating in the clinical trial. Retraining of the investigators will be conducted if deviations from recommended use are noted or updates to the IFU are implemented.
- The compliance of clinical sites to the protocol will be monitored. Corrective and preventative actions will be implemented based on the nature and number of protocol deviations observed

13.2.1 Device Design

The design of the MitraClip System includes many features aimed at minimizing potential risks. The major safety features of the device are described below:

- The MitraClip device is designed with the ability to grasp, capture and release the mitral valve leaflets. This can be performed repeatedly to reposition the device to optimize MR reduction. When MR reduction is acceptable, the device is deployed. If acceptable MR reduction is not achieved, the steps can be reversed and the device is not implanted.
- The MitraClip device is designed with a series of frictional elements that engage the surface of the leaflets to capture and retain the leaflets.
- The MitraClip device is intended to capture and independently retain two leaflets. In the event the device is not properly attached or detaches from one leaflet, capture of the opposing leaflet by the device reduces the likelihood of device embolization.
- The MitraClip device is covered with polyester fabric to promote tissue in-growth which anchors the device to the leaflets.

- The MitraClip device has been designed to withstand the forces exerted on it during the cardiac cycle and the device is constructed from well-characterized, biocompatible materials that have undergone extensive testing. Chronic animal studies, FEA (finite element analysis) modeling, and accelerated fatigue testing has established an acceptable fatigue life of the MitraClip device.
- Three distinct detachment mechanisms requiring multiple steps are required to fully deploy the device from the delivery catheter.
- The device is designed to be atraumatic to the valve tissue to minimize the risk of altering future surgical repair options.

13.2.2 Investigator Selection and Training

Only operators (must be investigators) who are skilled in the manipulation of catheter-based technology in the vasculature and heart, and have a good understanding of the risks associated with these manipulations will be selected for this trial. In addition, site investigators will undergo training on the techniques required to optimally place the device on the mitral leaflets.

As required, CT surgeons will have the training and support necessary to assist with device explant, if necessary. See **Section 10.7.1 Site Training** for additional details.

13.2.3 Ensuring Strict Adherence to the Clinical Investigational Plan

The COAPT Trial will be carefully monitored by the Sponsor monitor (or designee) to ensure adherence to the Clinical Investigational Plan. All adverse events and device deficiencies will be reported to Abbott Vascular and will be monitored internally for safety surveillance purposes.

13.2.4 Data Monitoring Committee (DMC)

A Data Monitoring Committee will review safety and effectiveness data. See **Section 10.5** for details.

13.3 Potential Benefit

Data obtained from previous clinical trials with the MitraClip device has shown that subjects experience (post-procedure) clinically and statistically significant improvements in quality of life, heart failure symptoms, functional capacity and left ventricular volumes and dimensions. Additional potential benefits of the use of the MitraClip System include, but may not be limited to, the following:

- Reduction in heart failure hospitalization rate
- Improved symptomatic status and quality of life
- Improved LV function as measured by reverse remodeling of the LV
- Reduced mortality

APPENDIX A: Definitions

The following definitions will be used in the COAPT Clinical Investigational Plan. All events constituting primary or secondary endpoints will be adjudicated by the independent Clinical Events Committee (except embolization, which will be site reported, and Mitral Valve Stenosis and SLDA, which will be assessed by Echocardiography Core Lab), along with relationship to the MitraClip device or procedure.

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.

CARDIOVASCULAR DEATH (VARC)

Cardiovascular death is defined by the Valve Academic Research Consortium (VARC)¹⁹ 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

¹⁹ Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol* 2011;57:253-269.

DEVICE OR PROCEDURE RELATED ADVERSE EVENT

Adverse events that are adjudicated by the Clinical Events Committee as probably, possibly or definitely device and/or procedure related, regardless of temporal relationship to the MitraClip procedure. For events reported by the site that are not adjudicated by the Clinical Events Committee, the device relationship will be reported based on site reports.

Examples of device-related adverse events 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.

MITRACLIP DEVICE EMBOLIZATION

Detachment of the deployed MitraClip device from both mitral leaflets.

ENDOCARDITIS

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

| |
|--|
| <p>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)</p> |
| <p>Pathological Criteria</p> <p>Microorganisms: culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, or</p> <p>Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis</p> <p>OR</p> <p>Clinical Criteria</p> <p>Major Criteria</p> <p><u>Persistently positive blood cultures:</u> Typical organisms for endocarditis: <i>Streptococcus viridans</i>, <i>S bovis</i>, “HACEK” group, community acquired <i>Staphylococcus aureus</i> or enterococci, in the absence of a primary focus</p> <p><u>Persistent bacteremia:</u> ≥ 2 positive cultures separated by ≥12 hours or ≥ 3 positive cultures ≥ 1 h apart or 70% blood culture samples positive if ≥ 4 are drawn</p> <p><u>Evidence of endocardial involvement</u></p> |

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

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

EXTREMELY HIGH SURGICAL RISK

The subject has co-morbidities such that the calculated STS mortality risk by either the replacement or repair calculator is $\geq 8\%$, or the subject has one or more individual co-morbidities that result in extremely high predicted operative risk of stroke or death as determined by the Central Eligibility Committee.

FUNCTIONAL MITRAL REGURGITATION

Defined as 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 apparatus, except mild focal thickening thought to be related to aging. No leaflet flail or other evidence of degenerative MR may be present even in the presence of global or regional LV systolic dysfunction.

GUIDELINE DIRECTED MEDICAL THERAPY (GDMT)

Guideline Directed Medical Therapy (GDMT) is defined as per the 2013 ACCF/AHA Heart Failure Guidelines and specified below. As described in the guidelines,

randomized controlled trials in patients with heart failure have primarily enrolled patients with a reduced left ventricular ejection fraction (LVEF $\leq 35\%$ or $\leq 40\%$; i.e. heart failure with reduced EF). It is only in these patients that efficacious therapies have been demonstrated to date. Importantly, patients may also develop symptomatic heart failure with “borderline” EF (LVEF of 41% to 49%). Many heart failure specialists choose to use the same medications at the same target doses to treat patients with borderline EF, especially those with severe MR, as they use to treat reduced EF patients. Therefore, GDMT as defined below for patients with reduced EF will be applied for patients with preserved EF in the current study.

Note: subjects must be on **maximum tolerated dose**, i.e., maximum dose unless the subject has documented intolerance to the maximum dose.

| Drug Class | Drug Name | INITIAL Daily Dose(s) | MAXIMUM Daily Dose(s) |
|--|--|--|--|
| ACE-Inhibitors (ACE-I) | Captopril | 6.25 mg TID | 50 mg TID |
| | Enalapril | 2.5 mg BID | 10 to 20 mg BID |
| | Fosinopril | 5 to 10 mg QD | 40 mg QD |
| | Lisinopril | 2.5 to 5 mg QD | 20 to 40 mg QD |
| | Perindopril | 2 mg QD | 8 to 16 mg QD |
| | Quinapril | 5 mg BID | 20 mg BID |
| | Ramipril | 1.25 to 2.5 mg QD | 10 mg QD |
| | Trandolapril | 1 mg QD | 4 mg QD |
| Angiotensin-Receptor Blocker (ARB) | Candesartan | 4 to 8 mg QD | 32 mg QD |
| | Losartan | 25 to 50 mg QD | 50 to 150 mg QD |
| | Valsartan | 20 to 40 mg BID | 160 mg BID |
| Aldosterone Antagonists | Spironolactone | 12.5 to 25 mg QD | 25 mg QD or BID |
| | Eplerenone | 25 mg QD | 50 mg QD |
| Beta-Blockers | Bisoprolol | 1.25 mg QD | 10 mg QD |
| | Carvedilol | 3.125 mg BID | 25 mg BID if subject is <85kgs* 50 mg BID if subject is >85kgs* |
| | Carvedilol Controlled Release | 10 mg QD | 80 mg QD |
| | Metoprolol succinate extended release | 12.5 to 25 mg QD | 200 mg QD |
| Vasodilators (nitrate and hydralazine): | Fixed dose combination (424) | 37.5 mg hydralazine / 20 mg isosorbide dinitrate TID | 75 mg hydralazine / 40 mg isosorbide dinitrate TID |
| | Hydralazine + isosorbide dinitrate (429) | Hydralazine: 25 to 50 mg (TID or QID) + isosorbide dinitrate: 20 to 30 mg (TID or QID) | Hydralazine: 300 mg (QD in divided doses) + isosorbide dinitrate: 120 mg (QD in divided doses) |

This minimally includes an ACE-inhibitor (ACE-I) at stable doses for 30 days prior to subject registration in the trial, if tolerated, and a beta blocker (carvedilol, sustained release metoprolol succinate, or bisoprolol) for 90 days prior to subject registration in the trial, if tolerated, with a stable up-titrated dose for 30 days prior to subject

registration in the trial. This also includes an Angiotensin II Receptor Blocker (ARB) at stable doses for 30 days prior to subject registration in the trial, if tolerated, when ACE-I is not tolerated. Stable is defined as no more than a 100% increase or a 50% decrease in dose.

If the subject is intolerant to ACE-I, ARB, or beta blockers, documented evidence must be available. In those intolerant to both ACE-I and ARB, combination therapy with hydralazine and oral nitrate should be considered. Therapeutic equivalence for ACE-I substitutions is allowed within the trial registration stability timelines. Aldosterone receptor antagonists [or mineralocorticoid receptor antagonists] are recommended in patients with NYHA class II-IV heart failure and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. If aldosterone inhibitor therapy is to be administered, it must be initiated and optimized at least 30 days prior to trial registration. Stability criteria are the same as for other neurohormonal antagonists. Eplerenone requires dosage stability for 30 days prior to subject registration in the trial similar to the other agents. Diuretics may be used as necessary to keep the subject euvolemic. All heart failure therapeutics and dosages should be documented in the electronic case report forms.

As described in the 2013 ACCF/AHA Heart Failure Guidelines, randomized controlled trials in patients with heart failure have primarily enrolled patients with a reduced left ventricular ejection fraction (LVEF $\leq 35\%$ or $\leq 40\%$; i.e. heart failure with reduced EF). It is only in these patients that efficacious therapies have been demonstrated to date.

However, patients may also develop symptomatic heart failure with “borderline” EF (LVEF of 41% to 49%). Many Heart Failure Specialists choose to use the same medications at the same target doses to treat patients with borderline ejection fraction, especially those with severe MR, as they use to treat reduced EF patients; therefore, GDMT as defined for patients with reduced EF will be applied for patients with preserved EF.

The Angiotensin Receptor-Nepriylsin Inhibitor (ARNI) Sacubitril/Valsartan (Entresto™) and the sinoatrial node modulator Ivabradine (Corlanor™) may be used as specified in the 2016 update* to the 2013 ACCF/AHA Guideline for the Management of Heart Failure. Use of these two agents is not required. However, if used, these drugs must be applied in accordance with the CIP as any other major change of GDMT described in the CIP. Specifically, after a major change in medication or dose (and stabilization on the maximum dose tolerated), a TTE is required after 30 days to ensure that the subject still has symptomatic functional MR ($\geq 3+$), and meets all criteria for enrollment. Per the 2016 Guideline update, ACE-I remains a Class I indication, and a subject should not be on both ACE-I and ARNI.

*Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016;68:1476-88.

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.

Hospitalizations will be adjudicated by the Clinical Events Committee as Heart Failure or Other Cardiovascular hospitalization (see definitions below for Heart Failure and Other Cardiovascular hospitalizations).

HEART FAILURE HOSPITALIZATION

Defined as an event that meets the following criteria of either (A and B and C) or D:

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 Clinical Investigational Plan, overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, do not meet the Clinical Investigational Plan definition of hospitalization. All hospitalizations, including the index hospitalization for the MitraClip procedure, if complicated by acute worsening heart failure that would have prompted an admission to hospital for heart failure, AND requires intravenous or invasive treatment AND hospitalization is extended by 24 hours, as defined above, will also be considered a heart failure hospitalization. Elective heart failure “tune-ups” that occur following the MitraClip procedure and prolong hospitalization will not count as a heart failure hospitalization.

OR

D) Subject arrives in emergency department with clinical presentation meeting the criteria of heart failure, but dies in the emergency department before hospital admission.

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.

INDEX PROCEDURE

The procedure in which the MitraClip device implant is first attempted. First attempt of the MitraClip is when the subject is prepared for the procedure and groin is punctured for the transseptal procedure.

LOCAL SITE HEART TEAM

The Local Site Heart Team must consist of, at a minimum, the CT Surgeon and Heart Failure specialist investigators.

MAJOR BLEEDING

Major bleeding is defined as bleeding \geq Type 3 based on a modified Bleeding Academic Research Consortium (BARC)²⁰ 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

²⁰ Mehrana R, Rao SV, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-2747.

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

MITRAL VALVE STENOSIS

Defined as a mitral valve orifice area of less than 1.5 cm² as measured by the Echocardiography Core Laboratory.

MODIFIED RANKIN SCALE SCORE DESCRIPTIONS

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

MITRACLIP PROCEDURE ATTEMPT

Defined as administration of anesthesia for the MitraClip procedure.

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) $\geq 10x$ ULN within 72 hrs. post-MitraClip procedure in patient with normal baseline CK-MB

OR

Mandatory: CK-MB $\geq 5x$ 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 $\geq 10x$ 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) - this definition also applies to Control group subjects or Device group subjects who do not undergo the 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. |
| 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-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.

NON-ELECTIVE (i.e., URGENT or EMERGENT) CARDIOVASCULAR SURGERY for DEVICE RELATED COMPLICATIONS

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.

OPTIMAL THERAPY

Subjects with current or prior symptoms of heart failure and reduced LVEF should be on stable, optimal standard of care therapy according to current guidelines for heart failure in the United States. This includes Guideline Directed Medical Therapy (GDMT) defined as per the 2013 ACCF/AHA Heart Failure Guidelines (see definition for Guideline Directed Medical Therapy).

Additionally, it is recognized that approximately two-thirds of patients with HF have underlying CAD (ischemic cardiomyopathy). Therefore, it is imperative that appropriate treatment for CAD be used in COAPT, according to the ACC/AHA Guidelines for Heart Failure. Specific recommendations listed in those guidelines are listed as follows:

- Use of nitrates and beta blockers for the treatment of angina,
- Coronary revascularization according to recommended guidelines in patients who have both HF and angina,
- Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina,
- Use of antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease

Subjects registered in COAPT should be treated with ICD and or CRT, as per the following guidelines, prior to subject registration in the trial:

- An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in subjects with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia.
- Implantable cardioverter-defibrillator therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in subjects with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, a LVEF less than or equal to 35%, and NYHA functional class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year
- Subjects with LVEF of less than or equal to 35%, sinus rhythm, left bundle-branch block (LBBB), a QRS duration of ≥ 150 ms, and NYHA functional class III or ambulatory class IV symptoms despite recommended optimal medical therapy, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated

In addition, revascularization (i.e., percutaneous coronary intervention, etc.) should occur prior to subject registration in the trial as applicable.

QUALIFYING TRANSTHORACIC ECHOCARDIOGRAM (TTE)

Qualifying TTE is defined as the TTE performed within 90 day prior to subject registration for confirmation of MR severity by the ECL.

PROLONGED VENTILATION

Defined as pulmonary insufficiency requiring ventilatory support for greater than 48 hours post-catheterization.

SERIOUS ADVERSE EVENT (SAE)

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

- a) Led to a death,
- b) Led to a serious deterioration in health that either:
 - 1) Resulted in a life-threatening illness or injury, or
 - 2) Resulted in a permanent impairment of a body structure or a body function, or
 - 3) Required in-patient hospitalization or prolongation of existing hospitalization, or
 - 4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.
- d) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, 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.

The assessment of disability resulting from the stroke will be performed by the modified Rankin Scale (mRS). Assessment of the mRS should occur at all scheduled visits through 24 months and at 90 days after stroke onset. This approach will maximize the detection of new strokes, assist in ongoing evaluation of events previously determined to be TIAs, and provide an accepted and reliable indicator of the long-term impact of a given stroke. A disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of 2 or more and in an increase of at least one mRS category from the individual's pre-stroke baseline. A non-disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of less than 2 or that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline.

Although imaging (typically, MRI for acute and chronic ischemia and haemorrhage, and CT for acute and chronic haemorrhage 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,

| |
|--|
| <p>infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist*</p> <p>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</p> |
| <p>Stroke classification</p> <p>Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue</p> <p>Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage</p> <p>A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic</p> |
| <p>Stroke definitions†</p> <p>Disabling stroke – a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual’s pre-stroke baseline</p> <p>Non-disabling stroke – a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual’s pre-stroke baseline</p> |

*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).

†Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

Unanticipated serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was **not previously identified in nature, severity, or degree of incidence** in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UNPLANNED HEART FAILURE VISIT

An "unplanned heart failure visit" is considered to include unscheduled office visits or Emergency Department (ED) visits that meet the definition for Heart Failure hospitalization, with the exception of the 24 hour requirement.

VULNERABLE POPULATION (ISO14155 Definition)

Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those permanently incapable of giving informed consent. Vulnerable populations also may include 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.

APPENDIX B: Echocardiography Protocol

Inclusion criteria and study endpoints will be determined with serial echocardiography performed at the individual investigational sites and interpreted at the Echocardiography Core Laboratory (ECL). The independent ECL will be responsible for the review and assessment of all echocardiograms obtained on registered subjects. The following guidelines should be followed for study echocardiograms. Site echocardiographic analysis will be performed by the Site's Echo Investigator. All measures required by the eCRF should be completed or noted when not possible.

I. General Echocardiographic Procedures

1. The EKG signal should be clearly visible on all frames.
2. Echocardiograms should be identified by the subject number assigned for the purpose of the trial. The eCRF will identify subject number and the date of the visit.
3. Echocardiographic images will be acquired and exported/transferred in digital format and saved as a DICOM image.
4. Height will be measured at the time of the first echocardiogram and weight will be measured and recorded on the eCRF at the time of each echocardiogram.
5. Blood pressure and heart rate will be recorded at the start of the echo study on the echo worksheet.
6. Variance maps should be turned off for the study.
7. An intravenous catheter may be placed for administration of left-sided contrast agent if needed for visualization of endocardial borders to enable accurate measurement of LV volumes. If a contrast agent is used for the baseline echocardiogram, it should also be used for all subsequent follow-up echocardiograms.
8. Site will provide a completed worksheet to accompany the digital DICOM echocardiogram for each echo study. For purposes of quality control, the site personnel are instructed to make and record all of the measurements and calculations required on the worksheet for reference for each screening echo study.
9. It is recommended that each site identify a single sonographer to perform all echo studies for a single subject, and that one echocardiography system be used for the image acquisition to the extent possible.

II. Echocardiographic Protocol for Image Acquisition

For the echocardiogram, the patient will be positioned in left lateral recumbency or in the position that permits optimal imaging. It is strongly recommended that an echocardiography bed with a dropout be used if available. With digital archiving, at least 3 cardiac cycles for normal sinus rhythm or paced, and at least 5 cardiac cycles for Afib are requested. Unless otherwise specified, depth should be adjusted to maximize the image while including all necessary structures. All images will be acquired at end-expiration held during quiet respiration. Harmonic imaging should be employed to optimize visualization of endocardial borders. All spectral pulsed wave (PW) and continuous wave (CW) Doppler will be performed at a sweep speed of 100 mm/sec. Color Doppler Nyquist limits will be adjusted to the range of 50 – 70 cm/sec, unless otherwise specified.

1. PLAX with and without magnification of the left ventricular outflow tract; with and without color flow Doppler interrogation of the aortic and mitral valves. Careful attention will be paid to identifying the vena contracta of the mitral regurgitant jet using zoom views. The vena contracta is the narrowest portion (or the “neck”) of the jet as it crosses the valve leaflets. The Nyquist limit should be set between 50 and 70 cm/sec and a zone of proximal jet acceleration should be identified on the ventricular aspect of the leaflets.
2. PSAX at the mid-papillary muscle level.
3. PSAX at the tips of the mitral valve leaflets to identify the minimum diastolic orifice of the mitral valve. When a MitraClip implant is present each mitral valve orifice should be imaged separately.
4. PSAX at the level of the mitral valve when both anterior and posterior leaflets are visualized. Position the Color Doppler scan box over the mitral orifice to visualize the regurgitant jet origin.
5. Basal PSAX (at the aortic valve level). Pulsed Doppler sample of pulmonary flow at the level of the pulmonary valve to measure pulmonary velocity time interval (VTI) opening and closing transients of the pulmonary valve should be recorded. Optimization of the pulmonary valve annulus for measurement of the pulmonary annular diameter.
6. Apical 4-chamber view, with and without color flow interrogation of mitral and tricuspid valves. The color flow Doppler interrogation should include the entire left atrium taking care to include wall-impinging eccentric jets in the region of interest. Gain should be adjusted to reduce excess noise. Spectral Doppler interrogation in this view includes:
 - a. PW Doppler of mitral inflow at mitral leaflet tips.

- b. PW Doppler of mitral inflow at the level of the mitral annulus at end-diastole with a small sample volume.
 - c. CW of the mitral inflow signal.
 - d. CW of the mitral regurgitant jet with care to record a complete signal and maximize the peak velocity. Contrast should be used to enhance this signal when incomplete and when a peak velocity cannot be determined. NOTE: Occasionally eccentric CW jets may require interrogation of additional views (EG. PLAX, Apical 2C view) to obtain the true maximal jet velocity.
 - e. CW of tricuspid regurgitant jet for estimation of pulmonary artery systolic pressure. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).
 - f. PW Doppler of right pulmonary vein flow. The sample volume should be placed at least 1 cm within the pulmonary vein, if possible. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).
 - g. Color flow Doppler visualization of PISA (proximal isovelocity surface area) using zoomed views for estimation of regurgitant orifice area. The Nyquist limit will be lowered and the baseline shifted in the direction of flow (toward left atrium) to maximize the PISA signal. The PISA aliasing velocity should be set to optimize the hemispheric shape of the proximal flow convergence region (usually 30-40 cm).
7. Anteriorly angulated 4-chamber view:
- a. Color flow Doppler to exclude aortic insufficiency. If present, aortic insufficiency jet will be optimized to permit measurement of the pressure half time using CW Doppler.
 - b. PW Doppler in left ventricular outflow tract positioned such that closing artifact but not opening artifact of the valve is visible.
 - c. CW Doppler through the aortic valve.
8. Apical 2-chamber view with and without color interrogation of the mitral valve.
9. Apical long-axis (also known as 3-chamber) view with and without color flow interrogation of the mitral valve. Zoom mode should also be used to identify the vena contracta and PISA in this view, as noted above.

10. Subcostal imaging of the inferior vena cava with and without a “sniff”.
11. Color Doppler of inter-atrial septum to interrogate presence of ASD.
12. Apical images of the left ventricle (LAX, 2- and 4-chamber views) should be collected taking care to minimize foreshortening.
13. Contrast will be used for endocardial border delineation when the endocardium is not well visualized on the harmonic image. For subjects with renal dysfunction, intravenous contrast should not be used during the procedure unless absolutely necessary. Contrast can also be employed for enhancement of the tricuspid regurgitant and pulmonary venous flow signals. During the contrast imaging, the mechanical index should be adjusted to avoid bubble destruction artifacts (usually a mechanical index of 0.3-0.5), and contrast infusion rate adjusted to avoid obliteration of the mitral annulus. Ideally, the focus should be set at the mitral annulus level. If a contrast agent is used for the baseline echocardiogram, it should also be used for all subsequent follow-up echocardiograms, unless subject experiences renal dysfunction.
14. For follow-up post-MitraClip implant, images of the MitraClip(s) in the following four views should be collected both with and without color Doppler to verify MitraClip position:
 - a. SAX – non-oblique at the Mitral Valve level
 - b. PLAX
 - c. Apical 4-chamber and long-axis
 - d. Anterior and posterior Intercommissural (IC) images

APPENDIX C: Monitoring Exposure to Ionizing Radiation

(1) Implanting Investigator Training

Prior to treating patients with the MitraClip device, all implanting investigators shall complete the MitraClip therapy training curriculum, including training to this section of the study Clinical Investigational Plan.

(2) Pre, Peri and Post-MitraClip Procedure

The implanting investigator shall be responsible for patient radiation levels and shall ensure that radiation dose accumulation is continuously monitored during the procedure (NCRP 2010). Documentation of dose levels shall be in accordance with the individual requirements of the respective institution's quality management program. In addition, the following shall apply:

a. Dose Measurements required for MitraClip procedure

Where the fluoroscopy system has the functionality for the output of data, the following dose measurements shall be recorded in the subject records and reported in the eCRFs.

- Total fluoro time: to be reported in minutes
- Total number of fluoro frames: to be reported as whole numbers, no associated units
- Air kerma-area product (P_{KA}) (dose area product): to be reported in $Gy\ cm^2$
- Air kerma at the reference point ($K_{a,r}$): to be reported in Gy
- Peak skin dose ($D_{skin, max}$): to be reported in Gy

Investigational centers that are unable to provide the information due to the limitations of their fluoroscopy systems are exempt from the reporting requirements.

b. Substantial Radiation Dose Level (SRDL)

The SRDL is a trigger level to initiate follow-up of a radiation dose that may produce a clinically relevant injury in an average patient. Procedures, such as the MitraClip procedure, that are performed using biplane fluoroscopy systems are a special situation because the dose received from each plane should be considered independently when the fields do not overlap. When they do overlap, the doses are additive and if it is uncertain whether the fields overlap, it should be assumed that they do.

The following are suggested values for first and subsequent notifications and the SRDL based upon a 100cm² field at the subject’s skin. The implanting investigator should adjust the notifications and the SRDL proportionally to the actual procedural field size. When the SRDL has been exceeded, the implanting investigator shall document the dose exceeded and the justification for the radiation dose level used (NCRP 2010).

Suggested values for first and subsequent notifications and the SRDL (NCRP 2010)

| Dose Metric | First Notification | Subsequent Notifications (increments) | SRDL |
|------------------|--------------------------|---------------------------------------|--------------------------|
| $D_{skin,max}$ | 2 Gy | 0.5 Gy | 3 Gy |
| Ka,r | 3 Gy | 1 Gy | 5 Gy |
| P_{KA} | 300 Gy cm ² * | 100 Gy cm ² * | 500 Gy cm ² * |
| Fluoroscopy time | 30 min | 15 min | 60 min |

* Assuming a 100 cm² field at the subject’s skin. For other field sizes, the P_{KA} values should be adjusted proportionally to the actual procedural field size (e.g., for a field size of 50 cm², the SRDL value for P_{KA} would be 250 Gy cm²).

i. Acute Evaluation

Subjects should be advised of the possibility of a skin injury due to a tissue reaction, and should be told to examine the beam entrance site at 2-4 weeks after the procedure and report any observations to the site Principal Investigator or designee. During the 7-day phone follow-up, the subject should be asked whether the subject has experienced a skin injury at or near the beam entrance site. During the physical examination at the 30-day follow-up clinic visit, the site Principal Investigator or designee shall examine the integrity of the subject’s skin at or near the beam entrance site. If there is evidence of skin injury, the site Principal Investigator or designee shall report it as an adverse event in accordance with the adverse event reporting requirements.

ii. Long-term Evaluation

The site Principal Investigator or designee is responsible for the ongoing collection and monitoring of radiation doses. An examination of the subject’s skin at or near the beam entrance site shall be performed by the site Principal Investigator or designee. If skin injury resulting from radiation exposure during the MitraClip procedure is ongoing beyond the 30-day follow-up, the site Principal Investigator or designee should arrange for follow-up care. Observations of skin injury shall be reported as an adverse event in accordance with the adverse event reporting requirements.

APPENDIX D: Components of Frailty

The following components of Frailty Index will be collected at baseline but will not be utilized to screen subjects for the trial. The assessment can be administered by either an investigator or research coordinator.

1. Date of assessment _____ / _____ / _____ (DD/MON/YYYY)

2. Katz activities of daily living: Activities of Daily Living is assessed based on an evaluation of the functional independence or dependence of patients in bathing, dressing, going to toilet, transferring, continence, and feeding. Assess the following:

| | |
|-----------------------------|--|
| BATHING - check one | <ul style="list-style-type: none"> Subject bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity. Subject needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing. |
| DRESSING - check one | <ul style="list-style-type: none"> Subject gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes. Subject needs help with dressing self or needs to be completely dressed. |
| TOILETING - check one | <ul style="list-style-type: none"> Subject goes to toilet, gets on and off, arranges clothes, cleans genital area without help. Subject needs help transferring to the toilet, cleaning self or uses bedpan or commode. |
| TRANSFERRING - check one | <ul style="list-style-type: none"> Subject moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable. Subject needs help in moving from bed to chair or requires a complete |
| CONTINENCE - check one | <ul style="list-style-type: none"> Subject exercises complete self-control over urination and defecation. Subject is partially or totally incontinent of bowel or bladder. |
| FEEDING - check one | <ul style="list-style-type: none"> Subject gets food from plate into mouth without help. Preparation of food may be done by another person. Subject needs partial or total help with feeding or requires parenteral feeding. |

3. Grip strength: The grip strength test is used to determine the strength in each of the subject's hands.

Procedure:

Equipment: Hand Dynamometer (will be provided by Sponsor if not available at the site)

- i. Illustrate the use of the instrument to the subject prior to testing.

- ii. The subject should be in a seated position. Elbow should be at a 90 degree angle, with arm not resting on table or “pinned” against chest wall.
 - iii. Ask the subject to squeeze the dynamometer with as much force as possible with the dominant hand, being careful to squeeze only once for each measurement.
 - iv. Three trials should be made with a pause of about 10-20 seconds between each trial to avoid muscle fatigue.
 - v. The grip strength in each of the 3 trials should be reported on the case report form.
4. 15-foot Gait Test: The Gait Test measures, in seconds, the time a person takes walk 15 feet

Procedure:

- i. Accompany the subject to the designated area, which should be well-lit, unobstructed, and contain clearly indicated markings at 0 and 15 feet
- ii. Position the subject with his/her feet behind and just touching the 0-foot start line
- iii. Instruct the subject to “**Walk at your comfortable pace**” until a few steps past the 15-foot mark (the subject should not start to slow down before the 15-foot mark)
- iv. Begin each trial on the word “**Go**”
- v. Start the timer with the first footfall after the 0-meter line
- vi. Stop the timer with the first footfall after the 15-foot line
- vii. Repeat 3 times, allowing sufficient time for recuperation between trials. Record the time taken to walk 15 feet on each of 3 trials. If subject is unable to walk 15 feet, record the reason.

Note: Subject may use a walking aid (cane, walker). If the subject is receiving an intravenous (IV) drip, he/she should perform the test without the IV only if it can be interrupted temporarily without any potential risk to the subject, if not, then the subject may perform the test pushing the IV pole.

APPENDIX E: ATS 6 Minute Walk Test Guidelines

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS
MARCH 2002

CONTENTS

- Purpose and Scope
- Background
- Indications and Limitations
- Contraindications
- Safety Issues
- Technical Aspects of the 6-Minute Walk Test
- Required Equipment
- Patient Preparation
- Measurements
- Quality Assurance
- Interpretation
- References

PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardio-

pulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (see Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

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Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation ($r = 0.73$) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41–43). Questionnaire indices of functional status have a larger short-term variability (22–33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44–47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocar-

dial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale

Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons (31, 48–50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

| | |
|--|----------|
| Pretreatment and posttreatment comparisons | |
| Lung transplantation | (9, 10) |
| Lung resection | (11) |
| Lung volume reduction surgery | (12, 13) |
| Pulmonary rehabilitation | (14, 15) |
| COPD | (16–18) |
| Pulmonary hypertension | |
| Heart failure | (19, 20) |
| Functional status (single measurement) | |
| COPD | (21, 22) |
| Cystic fibrosis | (23, 24) |
| Heart failure | (25–27) |
| Peripheral vascular disease | (28, 29) |
| Fibromyalgia | (30) |
| Older patients | (31) |
| Predictor of morbidity and mortality | |
| Heart failure | (32, 33) |
| COPD | (34, 35) |
| Primary pulmonary hypertension | (10, 36) |

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

TECHNICAL ASPECTS OF THE 6MWT

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Rationale. A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52–55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400–1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient’s usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A “warm-up” period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet (*see the APPENDIX*).

4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO₂) and follow manufacturer’s instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO₂ should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO₂. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a “fanny pack”) so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk. (57)

5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* Table 2 for the Borg scale and instructions [58]).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

“The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.”

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

“Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog.

Start now, or whenever you are ready.”

TABLE 2. THE BORG SCALE

| | |
|-----|-------------------------------------|
| 0 | Nothing at all |
| 0.5 | Very, very slight (just noticeable) |
| 1 | Very slight |
| 2 | Slight (light) |
| 3 | Moderate |
| 4 | Somewhat severe |
| 5 | Severe (heavy) |
| 6 | |
| 7 | Very severe |
| 8 | |
| 9 | |
| 10 | Very, very severe (maximal) |

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: “Please grade your level of shortness of breath using this scale.” Then ask this: “Please grade your level of fatigue using this scale.” At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO₂ and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWD variability (see Table 3). The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by fol-

lowing the standards found in this document and by using a quality-assurance program.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Rationale. The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Rationale. One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

Rationale. Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

| | |
|---|--|
| Factors reducing the 6MWD | |
| Shorter height | |
| Older age | |
| Higher body weight | |
| Female sex | |
| Impaired cognition | |
| A shorter corridor (more turns) | |
| Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease) | |
| Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI) | |
| Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.) | |
| Factors increasing the 6MWD | |
| Taller height (longer legs) | |
| Male sex | |
| High motivation | |
| A patient who has previously performed the test | |
| Medication for a disabling disease taken just before the test | |
| Oxygen supplementation in patients with exercise-induced hypoxemia | |

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended). Measurements of pulse and SpO₂ should be made after waiting at least 10 minutes after any change in oxygen delivery.

Rationale. For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

Medications

The type of medication, dose, and number of hours taken before the test should be noted.

Rationale. Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (1) an absolute value, (2) a percentage change, or (3) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking

an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle–arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

This statement was developed by the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.

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APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _____

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: _____ Race: _____ Height: _____ft _____in, _____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

| | Baseline | End of Test |
|------------------|-----------|--------------------|
| Time | ____:____ | ____:____ |
| Heart Rate | _____ | _____ |
| Dyspnea | _____ | _____ (Borg scale) |
| Fatigue | _____ | _____ (Borg scale) |
| SpO ₂ | _____ % | _____ % |

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: _____ (×60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____ %

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

APPENDIX F: Rates of Foreseeable Adverse Events

The potential risks associated with the MitraClip procedure are similar to those for standard cardiac catheterization techniques and the administration of anesthesia; however, all of the risks may not be known. Although anticipated risks are described below, due to the nature of this study, there may also be other risks, which are not known at this time. Additionally the risk of a device deficiency may occur, such as but not limited to; dislodgement of previously implanted devices and failure to retrieve MitraClip System components. The ability of the MitraClip device to maintain long term MR reduction is unknown.

The risks below have been grouped by expected seriousness, but may vary in seriousness. The risks associated with the MitraClip procedure include, but are not limited to, the following (rates are derived from a cohort of 351 high surgical risk patients undergoing the MitraClip procedure in US clinical trials and from global MitraClip experience for 2012):

1. Very Common: $\geq 10\%$: Nausea/ vomiting.
2. Common: $\geq 1.0\%$ to $<10\%$: Aneurysm or pseudo-aneurysm; Arrhythmias; Atrial fibrillation; Bleeding disorders including Coagulopathy or Hemorrhage requiring transfusion; Cardiac arrest; Cardiac perforation; Death; Edema (swelling or fluid accumulation); Fever or hyperthermia (high body temperature); Gastrointestinal bleeding or infarct; Hypotension/hypertension (low or high blood pressure); Infection; Pain; Mitral valve injury; Myocardial infarction; Prolonged angina; Pulmonary congestion; Renal insufficiency or failure; Shock, Anaphylactic or Cardiogenic; Single leaflet device attachment (SLDA); Stroke or transient ischemic attack (neurologic complication lasting <24 hours); Vascular trauma, dissection, or occlusion; Vessel perforation or laceration; Worsening heart failure.
3. Uncommon: $\geq 0.1\%$ to $<1.0\%$: Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex); Drug reaction to anti-platelet/anticoagulation agents/contrast media; Arterio-venous fistula; Atrial septal defect requiring intervention; Cardiac tamponade/Pericardial Effusion; Chordal entanglement/rupture; Conversion to standard valve surgery; Deep venous thrombosis (DVT); Dizziness, Dyspnea (shortness of breath); Emboli (air, thrombus, MitraClip device); Emergency cardiac surgery; Esophageal irritation; Esophageal perforation or stricture; Failure to deliver MitraClip to the intended site; Failure to retrieve MitraClip System or components; Hematoma; Infection; Septicemia; Injury to mitral valve complicating or preventing later surgical repair; MitraClip erosion, migration or malposition; Multi-system organ failure; Peripheral ischemia; Urinary tract infection; Vessel spasm; Worsening mitral regurgitation.
4. Rare: $\geq 0.01\%$ to $<0.1\%$: MitraClip Device thrombosis; MitraClip Device embolization; Prolonged ventilation (use of a breathing machine); Mitral stenosis; Respiratory failure/atelectasis (inability to expand the lungs fully)/pneumonia; Skin injury or tissue changes due to exposure to ionizing radiation.

5. Very Rare: < 0.01% (including not reported AEs): Dyskinesia; Endocarditis; Hemolysis; Lymphatic complications; Mesenteric ischemia; Pulmonary thromboembolism; Wound dehiscence.