



17-518: The MitraClip® EXPAND Study
A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip® Devices

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Planned Number of Sites and Region(s)	Up to 60 sites in Europe and the U.S.	
Abbott Medical Expert	[REDACTED] Director, Medical Affairs Structural Heart	
Study Type	Prospective, Multi-Center, Single-Arm, International, Post Market Observational Study	
Sponsor / Study Monitor	Abbott 3200 Lakeside Drive, Santa Clara, CA 95054	
Electronic Data Capture	ORACLE CLINICAL	
Core Laboratories	A core laboratory (core-lab) will be utilized to make echocardiographic assessments on a subset of patients enrolled into this study. The core-lab will be identified at a later stage of the study.	
Clinical Events Committee	An independent clinical events committee (CEC) will be established to adjudicate major adverse events in this study. The CEC will be established at a later stage of the study.	
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COMPLIANCE STATEMENT:

This Study will be conducted in accordance with this Protocol, the Declaration of Helsinki, applicable Good Clinical Practices and applicable regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, and OUS ISO14155) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the study will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective site and by the applicable regulatory authorities.

PROTOCOL SUMMARY

Protocol Name and Number	17-518: <i>The MitraClip® EXPAND Study</i>
Title	A contemporary, prospective study evaluating real-world experience of performance and safety for the next generation of MitraClip® devices (EXPAND)
Objectives	To confirm the safety and performance of the next generation MitraClip® NTR System and MitraClip® XTR System in a contemporary, real-world setting.
Devices	MitraClip® NTR and MitraClip® XTR Systems
Targeted number of subjects	Up to 1,000 subjects at a maximum of 60 sites in Europe and the US will be in <i>the MitraClip EXPAND Study</i> <i>The study will group subjects into cohorts for analysis based upon pre-determined anatomical characteristics.</i>
Study Design	Prospective, Multi-Center, Single-Arm, International, Post Market, Observational Study
Endpoints	<p><u>Safety</u></p> <ul style="list-style-type: none"> Major Adverse Events (MAE) at 30 days <p><u>Performance</u></p> <ul style="list-style-type: none"> Mitral Regurgitation (MR) Reduction to $\leq 2+$ at 30 days <p><u>Acute Measures:</u></p> <ul style="list-style-type: none"> Acute Procedural Success (APS) Acute Device Success Procedure Time Device Time Number of Clips Implanted Number of Attempted Grasps Use of MitraClip NTR or MitraClip XTR Device-Related Complications User Feedback In-hospital MAE MR Reduction to $\leq 1+$ at 30 days <p><u>Clinical Measures (Discharge, 1, 6 and 12 months):</u></p> <ul style="list-style-type: none"> All-cause Mortality Heart Failure Hospitalization MAE Device-Related Complications <p><u>Functional improvement Measures (Baseline, Discharge & 12 months):</u></p> <ul style="list-style-type: none"> New York Heart Association (NYHA) class improvement Quality of Life (QOL) improvement conducted by Kansas City Cardiomyopathy Questionnaire (KCCQ)

	<p><u>Echo Measures (Baseline, Post Procedure, 1, & 12 months):</u> Based on Site Reported Echocardiogram data for all subjects</p> <ul style="list-style-type: none"> • MR Severity Grade • Effective Regurgitant Orifice Area (EROA) • Coaptation Measures (length and depth) • Flail Measures (gap and width) • Grasping Area Anatomy • Chordal Support • Regurgitant Jet(s) Position and Quantity • Tricuspid Regurgitant (TR) Severity <p><u>Core Lab Subgroup:</u> Echocardiograms from a minimum of 100 subjects will be sent to a Core Lab for assessment</p>
Subject Follow-up	<p><u>Echocardiogram:</u> Discharge, 30 days and 12 Months <u>Clinical Visit:</u> 30 days and 12 Months <u>Phone Call:</u> 6 Months</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Subjects who give consent for study participation 2. Subjects scheduled to receive the MitraClip per the current approved indications for use 3. Subjects with Symptomatic MR (≥3+)
Exclusion Criteria	<ol style="list-style-type: none"> 1. Subjects participating in another clinical study that may impact the follow-up or results of this study.

1.0 INTRODUCTION

The MitraClip® System received Conformité Européene approval (CE Mark) in 2008 and US Food and Drug administration (FDA) Approval in 2013 for percutaneous treatment of patients with mitral regurgitation (MR). MR stems from two main etiologies: degenerative MR (DMR), characterized by a prolapse or flail of one or more segments of the mitral leaflets and functional MR (FMR), which manifests as a malcoaptation of leaflets caused by localized or generalized dysfunction / scarring of the left ventricle. The MitraClip is implanted during a procedure with echocardiographic and fluoroscopic guidance while the patient is under general anesthesia. A trans-septal catheterization is performed to access the left heart and the guide catheter is then percutaneously inserted into the femoral vein. The MitraClip device is positioned and then used to grasp and join the mitral valve leaflets at the maximum coaptation location resulting in fixed approximation of the mitral leaflets.^{1,2}

The MitraClip System has been shown to be safe and effective in over 4,500 patients in clinical trials and more than 50,000 patients in worldwide use to date. Abbott is now introducing the next generation MitraClip NTR and MitraClip XTR Systems. Both of these systems have an update that adds a modification to the delivery catheter of the current MitraClip NT System. The MitraClip XTR System also introduces an additional implant size which has longer arms on the clip implant that are designed to assist with grasping of the mitral leaflets. The MitraClip NTR and MitraClip XTR Systems have not yet been evaluated in a clinical study.

The MitraClip EXPAND Study (A Contemporary, Prospective, Multi-center Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) is designed to confirm the safety and performance of the MitraClip NTR System and MitraClip XTR System. The data collected in this study will be used to evaluate device outcomes and characterize trends in patient selection for MitraClip therapy in contemporary real-world use. Specifically, the analysis will separate patients into cohorts based on anatomical characteristics to compare modern day use to use in early clinical studies. Moreover, the data will be assessed to identify patient or mitral valve anatomical characteristics that may be most appropriate for these next generation devices. Clinical outcomes and Echocardiographic measures will be assessed in the context of historical data.

A subset of subjects in *the MitraClip EXPAND Study* will become part of the MitraClip XTR Post Market Clinical Follow-up (PMCF) Study (**Appendix I**). Data from the MitraClip XTR PMCF Study will be used to fulfill the regulatory requirement for PMCF associated with the CE mark approval of the MitraClip XTR System.

The MitraClip EXPAND Study will be conducted on commercial MitraClip NTR System and MitraClip XTR System that have received CE Mark and/or FDA approval as required.

1.1 Study Design

This is a Prospective, Multi-Center, Single-Arm, International, Post Market, Observational Study designed to collect real-world data on the use of the next generation MitraClip NTR and MitraClip XTR Systems. Up to 1,000 commercial patients from the EU or US will be included in the analysis

¹ Kar, Saibal, The Percutaneous Valve Repair: Adding life to years, J Am Coll Cardiol. 2013 Sep 17;62(12):1062-1064

² Maisano, Francesco, Buzzatti, Nicola, Taramasso, Maurizio, and Alfieri, Ottavio, Mitral Transcatheter Technologies. Rambam Maimonides Medical Journal. July 2013, Volume 4, Issue 3, e0015

for *The MitraClip EXPAND Study*. Follow-up echocardiograms will be collected at 30 days and 12 months post-procedure visits with an additional clinical follow-up visit or phone call at 6 months.

The study will group subjects into cohorts for analysis based upon select pre-defined mitral valve anatomic criteria. This approach is supported by recent literature that shows an evolution of the use of MitraClip in which a significant percentage of cases presented in post-market studies differ in patient selection from the cases included in early clinical studies (ie. EVEREST, EVEREST II)^{3,4,5,6}. The analysis of these cohorts will allow for the evaluation of outcomes and identification of trends in patient selection and outcomes in contemporary real-world use in the context of historical MitraClip data.

1.2 Study Objective

The primary objective is to confirm the safety and performance of the next generation MitraClip® NTR and MitraClip® XTR Systems within a contemporary real-world setting.

2.0 BACKGROUND AND RATIONALE

2.1 Background

2.1.1 MitraClip® Clinical Trials Conducted for Approval

The MitraClip® System was studied in the United States as an investigational device beginning with the EVEREST I trial in July 2003 (IDE G030064). A total of 55 patients were enrolled. The EVEREST I Feasibility trial was the first prospective, multi-center trial to evaluate the safety and effectiveness of the MitraClip System in patients with 3+ or 4+ MR in surgical candidates. The trial demonstrated mechanistic feasibility of implant and safety of the MitraClip System and procedure. Acute procedural success was achieved in 70.9% of patients with a majority of patients (83.3%) experiencing a reduction in MR severity to 2+ or less at discharge. At 5 years, freedom from death was 86.4% and freedom from mitral valve surgery was 55.1%⁷.

³ A Study of the Evalve® Cardiovascular Valve Repair (MitraClip®) System Endovascular Valve Edge-to-Edge REpair Study

⁴ Boerlage-van Dijk K, et al, Mitral valve anatomy predicts outcome of MitraClip implantation, *Int J Cardiol* (2014)

⁵ Ambrožič J, Bervar M, Bunc M., *Wien Klin Wochenschr*. Initial Slovenian experience with MitraClip therapy: Careful selection of patients is crucial for optimal outcome. 2017 Dec 4. doi: 10.1007/s00508-017-1295-7. [Epub ahead of print]

⁶ Lesevic H, Karl M, Braun D, Barthel P, Orban M, Pache J, Hadamitzky M, Mehilli J, Stecher L, Massberg S, Ott I, Schunkert H, Kastrati A, Sonne C, Hausleiter J. Long-Term Outcomes after MitraClip Implantation According to the Presence or Absence of EVEREST Inclusion Criteria. *Am J Cardiol*. 2017; 119:1255-1261

⁷ IDE G030064/ P100009/A017 EVEREST I Final Clinical Report Version 1.0 - 17/Nov/2011

Following positive outcomes with the EVEREST I trial, EVEREST II was initiated. The EVEREST II Randomized Controlled Trial (RCT)^{8, 9, 10} was a prospective, multi-center, randomized controlled trial where patients with severe MR (3+ or 4+) were randomized in a 2:1 ratio to either receive the MitraClip device or undergo mitral valve surgery. The trial enrolled 279 patients: 184 treated with MitraClip and 95 with surgery. The trial met both primary safety and effectiveness endpoints. MR reduction to 2+ or less at 5 years was in 82.1% of MitraClip patients and 97.6% of surgery patients. Improvement in NYHA Functional Class was demonstrated in both groups, with 91.5% of MitraClip patients and 97.6% of surgery patients free from New York Heart Association (NYHA) Functional Class III or IV symptoms at 5 years. The results demonstrate the continued safety, durability of effectiveness and clinical benefit of the MitraClip device through 5 years¹¹.

The EVEREST II trial included a separate study to evaluate the safety and effectiveness of the MitraClip System in patients with 3+ or 4+ MR considered to be at high risk of surgical mortality. The EVEREST II High Risk Registry (HRR) study enrolled 78 patients at 25 centers. Implant success in the EVEREST II HRR was high with 96.2% of patients implanted with one (59.0%) or two (37.2%) MitraClip devices. At 5 years, MR reduction was sustained to $\leq 2+$ in 73.9% of surviving patients with paired data and to $\leq 1+$ in 47.8% of surviving patients with paired data. Through 5 years, a total of 42 (53.8%) deaths occurred in the EVEREST II HRR¹². This mortality rate is as expected due to the high risk nature of the patient population.

A continued access study, EVEREST II REALISM, sustained data collection on the use of the MitraClip System in “real world” conditions. There were two arms (High Risk and Non-High Risk) in the REALISM study. A total of 271 patients were enrolled in the non-high risk arm of REALISM. Reduction to MR $\leq 2+$ was achieved in 89% of patients at 30 days and in 84% of patients at 12 months. A similar trend was observed at subsequent follow-ups with a majority (>75%) of patients with MR severity remaining consistently mild to moderate¹³. A total of 628 patients were enrolled in the high risk arm of REALISM. A majority of patients had multiple pre-existing co-morbidities at baseline and were considered high risk for mitral valve surgery. Reduction of MR $\leq 2+$ was achieved in 90% of patients at discharge/30 days and in 85% of patients at 12 months. A similar trend was observed at subsequent follow-ups with a majority (>80%) of patients with MR severity remaining consistently mild to moderate¹⁴.

⁸ Mauri L, Garg P, Massaro JM, Foster E, Glower D, Mehoudar P, Powell F, Komtebedde J, McDermott E, Feldman T. The EVEREST II Trial: Design and Rationale for a Randomized Study of the Evalve MitraClip System Compared with Mitral Valve Surgery for Mitral Regurgitation. *Am Heart J.* 2010; 160:23-29.

⁹ Feldman T, Foster E, Glower DD, 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, Mauri L, Investigators EI. Percutaneous Repair or Surgery for Mitral Regurgitation. *N Engl J Med.* 2011; 364:1395-1406.

¹⁰ Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, Apruzzese P, Fail P, Rinaldi MJ, Smalling RW, Hermiller JB, Heimansohn D, Gray WA, Grayburn PA, Mack MJ, Lim DS, Ailawadi G, Herrmann HC, Acker MA, Silvestry FE, Foster E, Wang A, Glower DD, Mauri L, Investigators EI. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol.* 2015; 66:2844-2854.

¹¹ EVEREST II Randomized Controlled Trial (RCT) -0401– Five Year Final Report, Report Version 1.0 - 03/Nov/2014

¹² EVEREST II High Risk Registry (HRR) – 0401 - Five Year Final Report, Report Version 1.0 – 03/Nov/2014

¹³ EVEREST II REALISM– Non-High Risk 2017 Annual Report, Protocol #0401- Clinical Investigation Report Ver 1.0 - 24/APR/2017

¹⁴ EVEREST II REALISM– High Risk 2017 Annual Report, Protocol #0401- Clinical Investigation Report Ver 1.0 24/Apr/2017

2.1.2 MitraClip® Post-Market Clinical Studies

In 2008, based upon data from the EVEREST I study, the MitraClip® received CE mark approval for commercial use in Europe and was indicated for the reconstruction of the insufficient mitral valve for tissue approximation. Clinical evidence generated from EVEREST I, EVEREST II, EVEREST II HRR, and EVEREST II REALISM led to FDA approval in 2013 of the MitraClip® system for the treatment of patients with severe MR who are at prohibitive risk for surgery.

In the time since these approvals, a number of post-market clinical studies have been conducted on the MitraClip. All of these studies have provided continued evidence of the safety and performance of the MitraClip System. The studies for Europe and the US are summarized in the **Table 1**.

Table 1. Summary of Post-Market MitraClip® Studies

Study Reference	Study Design	Study Population	Study Outcome
Franzen et al. ¹⁵ Analysis from Hamburg University Heart Center	Examine MitraClip use in high surgical risk patients not meeting EVEREST criteria	51 subjects 35 (69%) would have been excluded from EVEREST I & II	MitraClip successful in treatment of patients outside of EVEREST criteria
ACCESS-EU ¹⁶ (EU study sponsored by Abbott)	Two-phase prospective, single-arm looking at health economics and clinical	567 subjects 77.1% FMR 84.9% NYHA III or IV High surgical risk	MitraClip implant success 99.6% 78.9 %MR reduction <2+ at 1yr Improved 6MWT, NYHA and QOL ¹⁷
Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation GRASP Registry ¹⁸	Prospective Single-center study at Ferrarotto Hospital in Catania, Italy. Site heart team led enrollment criteria	117 high surgical risk 76% FMR 98% MR3+/4+ 63% met EVEREST criteria	100% Acute procedural success Post Procedure MR Reduction 1+ (63%) 2+ (37%) KM Freedom from MAE 96.4% at 30 days and 75.8% at 1 yr
German TRanscatheter Mitral Valve Interventions (TRAMI) Registry	Had both prospective and retrospective enrollment.	828 prospective patients at 21 sites	97% implant success 1.4±0.6 clips/case 85.2% MR reduced to none/ mild Mortality 4.5% 1 m /20.3% 1 yr

¹⁵ Franzen O, Baldus S, Rudolph V, Meyer S, Knap M, Koschyk D, Treede H, Barmeyer A, Schofer J, Costard-Jackle A, Schluter M, Reichenspurner H, Meinertz T. Acute Outcomes of MitraClip Therapy for Mitral Regurgitation in High-Surgical-Risk Patients: Emphasis on Adverse Valve Morphology and Severe Left Ventricular Dysfunction. *Eur Heart J*. 2010; 31:1373-1381.

¹⁶ Maisano F, Franzen O, Baldus S, Schafer 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 1-Year Results from the ACCESS-EU, a Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe. *J Am Coll Cardiol*. 2013; 62:1052-1061.

¹⁷ ACCESS-EU Phase I Study Final Clinical Report, Version 1.0, 20/Aug/2012

¹⁸ Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistrutto A, Ministeri M, Barbanti M, Caggi A, Chiaranda M, Dipasqua F, Giaquinta S, Occhipinti M, Ussia G, Tamburino C. One- and Twelve-Month Safety and Efficacy Outcomes of Patients Undergoing Edge-to-Edge Percutaneous Mitral Valve Repair (from the GRASP Registry). *Am J Cardiol*. 2013; 111:1482-1487.

	Several TRAMI reports have been published ^{19,20}	(from the largest publication ²¹) 70%FMR 94% Severe MR	
The Transcatheter Valve Treatment Sentinel Pilot Registry ²²	European Society of Cardiology Euro Observational Research Programme conducted at 25 centers in 8 European countries	628 patients 72% FMR EuroSCORE 20.4±16.7% (indicates high risk)	95.4% Acute procedural success 98.2% MR Reduction ≤2+ post-procedure 94% MR Reduction ≤2+ at 1 yr 15.3% Mortality at 1 yr
TVT Registry (Transcatheter Valve Treatment) A Joint Initiative Society of Thoracic Surgeons (STS) & American College of Cardiology (ACC)	A platform for: 1) device and procedural surveillance; 2) quality assurance and improvement initiatives; and 3) efficient conduct of studies that will speed US access to new devices and support the expansion of device labeling	(Sorajja et al. ²³ -most recent publication) 2,952 patients at 145 sites 85.9% DMR 17.5% (FMR only 8.6%; mixed 8.9%). 93% MR 3+/ 4+ MR	93% MR reduction ≤2+ 61.8% MR grade ≤1+ 5.2% 30-day Mortality 37.9% 1 yr death and HF re-hospitalization (24.7% DMR)

2.1.3 Mitral Valve Anatomies: Impact on MitraClip Use and Outcomes

As the MitraClip therapy matures, there has been an increasing interest in exploring the potential for use in broader mitral valve anatomies. The recommended criteria were established early in MitraClip use during the EVEREST II Study. Some recent data have examined the true impact of these criteria on patient selection and MR outcomes; a few studies are described below.

Attizzani et al.²⁴ analyzed the outcomes of patients enrolled in the GRASP registry according to baseline echocardiographic criteria. A total of 78 patients that met EVEREST criteria (EVEREST_{on})

¹⁹ Baldus S, Schillinger W, Franzen O, Bekeredjian R, Sievert H, Schofer J, Kuck KH, Konorza T, Mollmann H, Hehrlein C, Ouarrak T, Senges J, Meinertz T, investigators GTMVI. MitraClip Therapy in Daily Clinical Practice: Initial Results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. *Eur J Heart Fail.* 2012; 14:1050-1055.

²⁰ Schillinger W, Hunlich M, Baldus S, Ouarrak T, Boekstegers P, Hink U, Butter C, Bekeredjian R, Plicht B, Sievert H, Schofer J, Senges J, Meinertz T, Hasenfuss G. Acute Outcomes after MitraClip Therapy in Highly Aged Patients: Results from German Transcatheter Mitral Valve Interventions (TRAMI) Registry. *EuroIntervention.* 2013; 9:84-90.

²¹ Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-Year Outcomes and Predictors of Mortality after MitraClip Therapy in Contemporary Clinical Practice: Results from the German Transcatheter Mitral Valve Interventions Registry. *Eur Heart J.* 2016; 37:703-712.

²² Therapy in Contemporary Clinical Practice: Results from the German Transcatheter Mitral Valve Interventions Registry. *Eur Heart J.* 2016; 37:703-712.

²³ Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR Jr, Stebbins A, Kar S, Thourani V, Ailawadi G. Outcomes With Transcatheter Mitral Valve Repair in the United States: An STS/ACC TVT Registry Report. *J Am Coll Cardiol.* 2017;70(19):2315-2327.

²⁴ Attizzani GF, Ohno Y, Capodanno D, Cannata S, Dipasqua F, Imme S, Mangiafico S, Barbanti M, Ministeri M, Cageggi A, Pistritto AM, Giaquinta S, Farruggio S, Chiaranda M, Ronsivalle G, Schnell A, Scandura S, Tamburino C, Capranzano P, Grasso C. Extended Use of Percutaneous Edge-to-Edge Mitral Valve Repair Beyond EVEREST (Endovascular Valve Edge-to-Edge Repair) Criteria: 30-Day and 12-Month Clinical and Echocardiographic Outcomes from the GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) Registry. *JACC Cardiovasc Interv.* 2015; 8:74-82.

were compared to 93 patients that did not meet EVEREST Criteria (EVEREST_{OFF}) which included 35 patients with LVEF \leq 25%, 28 patients with LV end systolic diameter $>$ 55 mm, 34 patients with coaptation depth \geq 11 mm, and 10 patients with a flail width \geq 15 mm. High rates of acute procedural success were achieved in both groups (97.8% and 100% for EVEREST_{OFF} and EVEREST_{ON}, respectively). At 30-days, the rate of MAEs (i.e. primary safety endpoint) was comparable between groups (2.6% vs. 6.5%, respectively, $p=0.204$). Reduction in MR severity, symptomatic improvements, and re-hospitalizations for heart failure were comparable between the two groups. At 1 year, Kaplan-Meier freedom from the freedom from death, surgery for mitral valve dysfunction, or grade \geq 3+ MR at 12 months was demonstrated in 71.4% and 76.2%, respectively, in the EVEREST_{OFF} and EVEREST_{ON} groups. Approximately 90% of surviving patients in both groups had sustained MR reduction to \leq 2+.

In more recent 2016 publication, Lesevic et al.²⁵ retrospectively analyzed patients treated with the MitraClip® device and compared the procedural success, long-term outcomes, repair durability, and prognostic factors. Patients were grouped into the EVEREST group (N=59) or non-EVEREST group (N=75) according to the presence or absence of EVEREST inclusion criteria. Acute procedural success was achieved in 95.5% of patients with no difference between EVEREST (97%) and non-EVEREST (95%) patients. There was no statistically significant difference in the number of device implanted between the two groups. A similar mean acute MR reduction was achieved in both groups (-2.3 ± 0.9 vs -2.2 ± 1 , respectively; $p=0.497$). At a mean follow-up of 3.5 years, recurring MR \geq 3+ was more frequent in non-EVEREST patients than in EVEREST patients (28% vs 45%; $p=0.066$). Re-interventions for recurring MR were more frequently required in non-EVEREST patients than in EVEREST patients, including second MitraClip device interventions (2% vs 13%; $p=0.085$) and mitral valve surgeries (9% vs 28%; $p=0.047$). Flail width was found to be an independent predictor for re-intervention, whereas flail gap \geq 10 mm displayed a strong trend (flail width: adjusted HR 11.2, 95% CI 2.6 to 48.3; $p=0.001$; flail gap: adjusted HR 3.1, 95% CI 0.9 to 11.5; $p=0.077$).

These data suggest that a closer look at the impact of mitral valve anatomy for MitraClip patient selection and outcomes is warranted to understand the appropriate real-world applications of the therapy. In the context of the introduction of the next generation MitraClip System, this analysis can be used to identify the mitral valve anatomical characteristics that may benefit most from the attributes of this device iteration (i.e. improved delivery and longer arms on the implant). This is the basis for the MitraClip EXPAND Study.

A full review of MitraClip studies and commercial literature was conducted and is shown in Appendix III.

2.2 Study Rationale

The primary objective of the MitraClip EXPAND study is to confirm the safety and performance of the MitraClip® NTR and MitraClip® XTR Systems in a contemporary real-world setting. The rationale for conducting this study is as follows:

- This study will provide first-hand clinical evidence of safety and performance of these next generation MitraClip Systems.
- This study will satisfy post-market clinical follow-up (PMCF) required as a condition of CE Mark approval for the MitraClip NTR and MitraClip XTR Systems. A subset of patients will be analyzed as part of the MitraClip XTR PMCF Study (Appendix 1) to fulfill this requirement.

²⁵ Lesevic H, Karl M, Braun D, Barthel P, Orban M, Pache J, Hadamitzky M, Mehilli J, Stecher L, Massberg S, Ott I, Schunkert H, Kastrati A, Sonne C, Hausleiter J. Long-Term Outcomes after MitraClip Implantation According to the Presence or Absence of EVEREST Inclusion Criteria. *Am J Cardiol.* 2017; 119:1255-1261.

- The device iterations on the MitraClip NTR (improved delivery) and MitraClip XTR (improved delivery and longer clip arms on implant) may offer an advantage in some mitral valve anatomies; this study will begin to identify populations that can benefit most from these next generation MitraClip Systems.
- Recent literature has indicated an evolution in patient selection in MitraClip therapy; this study will evaluate outcomes and characterize trends for MitraClip therapy in contemporary real-world use in the context of historical MitraClip data.

2.3 Summary of Device

2.3.1 Name of the Device

This study will include patients, who will undergo commercial procedures with the MitraClip® NTR System and/or MitraClip® XTR System after required approval of the device is obtained.

2.3.2 Indication for Use

MitraClip® procedures for this study will be conducted in accordance with the Instructions for Use (IFU) that is approved for the region where the implant is taking place.

2.3.3 Description of the Device

The MitraClip System is comprised of the Clip Delivery System (CDS) and Steerable Guide Catheter (SGC). The CDS is introduced into the body through the SGC. The Clip Delivery System is used to advance and manipulate the implantable clip 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 Steerable Guide Catheter provides a conduit to access the mitral valve and with the addition of Steerable Sleeve to position the Clip relative to the valve. The Delivery Catheter is designed to deliver and deploy the Clip. The Steerable Guide and Clip Delivery System are steered and actuated by the use of control knobs, levers and fasteners (**Figure 1**).

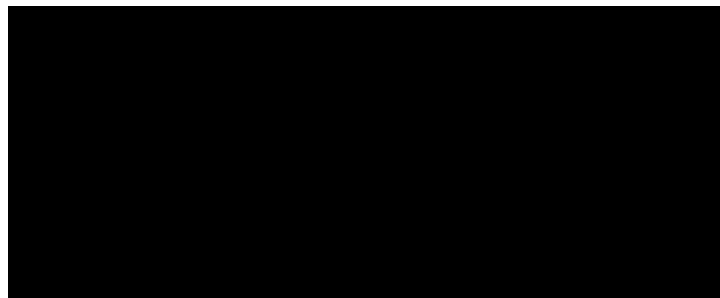


Figure 1. Proximal End of MitraClip NTR and MitraClip XTR Systems

The new MitraClip NTR System and MitraClip XTR System have a modification to the Delivery Catheter (DC) of the current MitraClip NT System intended to make the procedure easier, more precise, more predictable, and to optimize manufacturability of the product.

The implantable Clip is fabricated with metal alloys and polyester fabric that are commonly used in cardiovascular implants. The Clip can be repeatedly opened, closed and inverted by deliberate

manipulations of the Delivery Catheter Handle. The Clip positions are designed to allow the Clip to grasp and approximate the leaflets of the mitral valve.

The MitraClip XTR System has the same modified CDS as MitraClip NTR system but incorporates the additional implant size. Specifically, the arms on the implant of the MitraClip XTR System are longer than the clip implant in the MitraClip NTR System. This is intended to assist with leaflet grasping (**Figure 2**).

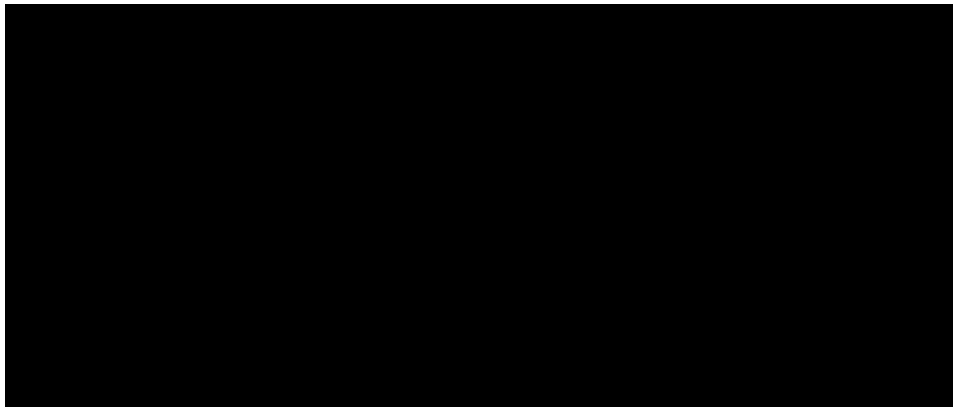


Figure 1. MitraClip NTR & MitraClip XTR Clip Implant

3.0 STUDY FLOW AND FOLLOW-UP SCHEDULE

3.1 Number of Subjects

Eligible consecutive patients that present for a MitraClip procedure should be consented. Once a patient has provided written informed consent, the patient is considered enrolled. Upon echocardiographic verification that there is no evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus per IFU requirements; the MitraClip procedure should be attempted for all enrolled patients. A procedure is considered attempted when the MitraClip delivery system is introduced into the femoral vein. Only enrolled patients with an attempted MitraClip procedure will be included in the analysis population. Patients that have an attempted procedure, but no MitraClip implant will be followed for 30 days only.

Patients that do not give consent or patients with a thrombus identified on the pre-treatment echocardiogram are not eligible for the EXPAND Study and will not be part of the analysis population. If the thrombus is medically treated and resolved at a later date, a patient may be re-consented for the EXPAND Study if they are eligible for a new attempted MitraClip procedure.

Up to 1,000 consented subjects with confirmation of no thrombus who have a MitraClip procedure attempted will be included for analysis in *the MitraClip EXPAND Study*. The Study will be conducted at a maximum of 60 centers in the EU and the US. A site maximum of 100 subjects will be enforced so that no site will be permitted to submit data for more than 10% of the study population.

3.2 Overall Flow of the Study and Follow-up Schedule

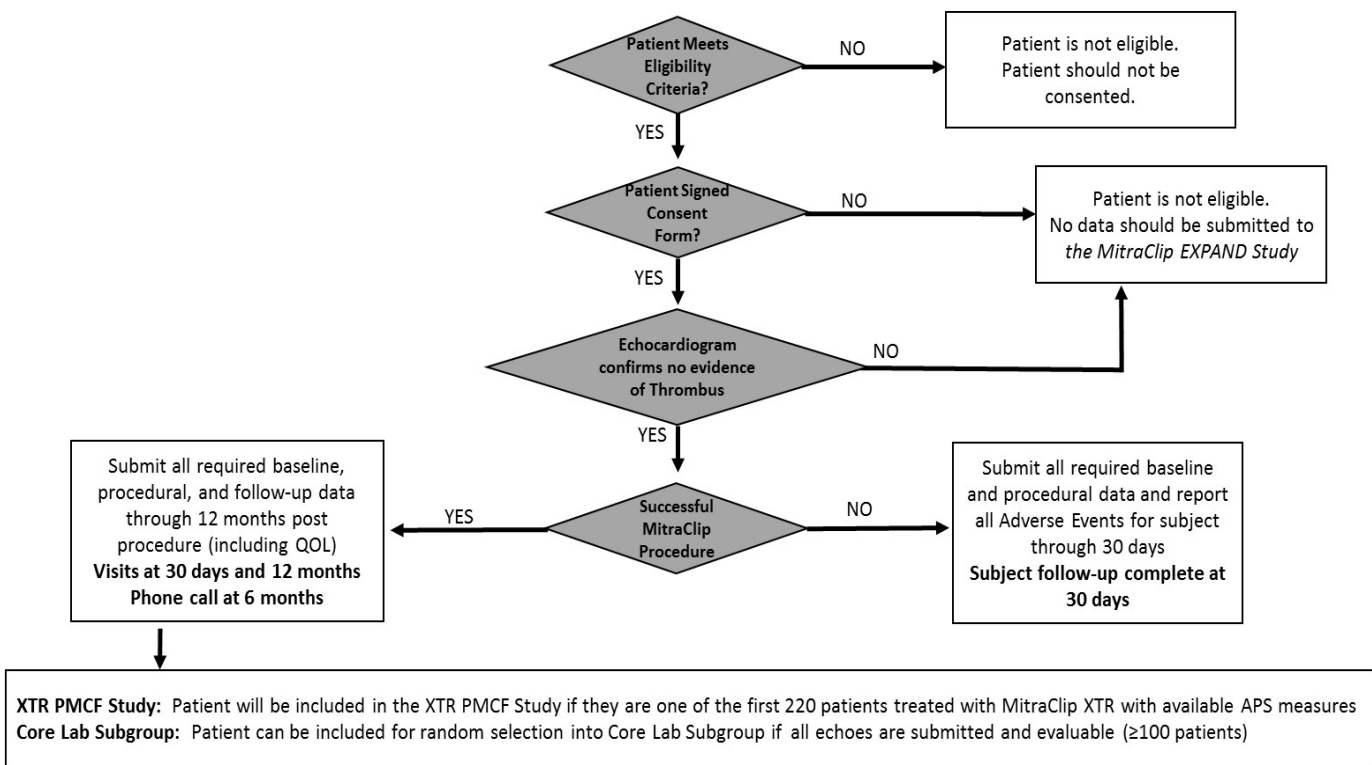
Enrolled patients that receive a MitraClip implant should undergo study follow-up per standard of care. Follow-up data on clinical assessment should be submitted for a 30-day visit, 6-month visit or phone call and 12-month visit. Echocardiograms are required to be submitted for the baseline, discharge, 30-day and 12-month time points. All Echocardiograms conducted during the study period (required by protocol or not) will be collected by the Sponsor (see **Table 2** for the Clinical Assessment Schedule). Patients that have an attempted procedure, but no MitraClip implant will be followed for 30 days only.

The first 220 European patients treated with the MitraClip XTR in *the MitraClip EXPAND Study* with evaluable APS data will be included in the XTR PMCF Study as described in Appendix 1.

Subjects with evaluable echocardiograms may be selected for a more detailed assessment by an independent core lab. Pre-defined criteria will be used to identify eligible subjects for this assessment. A minimum of 100 subjects will be randomly selected from this eligible population.

Figure 3 outlines the flow of the Study.

Figure 3: Study Flow



3.3 Measures Taken to Avoid and Minimize Bias

3.3.1 Study Flow

Study sites are instructed to consent consecutive subjects prior to MitraClip procedure. All patients eligible to receive a MitraClip (i.e. no evidence of thrombus) will included in the study analysis.

3.3.2 Clinical Events Committee

The safety endpoint for the study will include oversight by an independent CEC which will issue the final decision on reported MAEs.

3.3.3 Steering Committee

An independent steering committee will have oversight on the study.

3.4 Early Termination of the Clinical Study

No formal statistical rule for early termination of this study is defined.

The Sponsor reserves the right to discontinue the study at any stage or reduce the follow up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (UADE) occurs and it presents an unreasonable risk to the participating subjects.
- The Steering Committee makes a recommendation to stop or terminate the study

Should the study be discontinued by the Sponsor, patients will be followed up as per routine hospital practice with device related Adverse Events (AEs) being reported to the Sponsor as per vigilance/commercial reporting requirements.

In the event of study termination, the investigator shall return all clinical study materials to the Sponsor, and provide a written statement as to why the premature termination has taken place to the IRB/EC (if applicable). All applicable Clinical Investigation documents shall be subject to the same retention policy as detailed in section 12 of the Protocol entitled, 'Data Handling and Record Keeping'.

4.0 STUDY ENDPOINTS

4.1 Safety and Performance Measures

- Safety
The assessment of safety will include all occurrences through 30 days post procedure.
Occurrence of Major Adverse Events (MAE) at 30 days
MAE is defined as a composite of all-cause Death, Myocardial Infarction, Stroke, or non-elective Cardiovascular (CV) surgery for device related complications (CEC adjudicated).
- Performance
The assessment of performance measures will include all data reported at 30-day visits for this study.
MR Reduction to $\leq 2+$ at 30 days

4.2 Acute Measures

- Acute Procedural Success (APS) defined as successful implantation of the MitraClip® device with resulting MR severity of 2+ or less on discharge Echocardiogram (30-day

echocardiogram will be used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are considered to be an APS failure

- Acute Device Success defined as successful implant of the MitraClip device without the occurrence of a Device-Related Complication (including mitral valve stenosis, device embolization, Single Leaflet Device Attachment (SLDA), Iatrogenic atrial septal defect, or myocardial perforation) through discharge.
- Use of MitraClip NTR or MitraClip XTR: to include the percentage of cases with each device and an assessment of reason for device selection
- Procedure Time: defined as the time elapsed from the first intravascular catheter placement or trans-esophageal echocardiogram (TEE) to the removal of the last catheter and TEE
- Number of Clips Implanted
- Number of Attempted Grasps defined as the number of attempts to stabilize leaflets by the open Clip
- User feedback
- Device-Related Complications defined as the occurrence of one the following adverse events that is determined by investigator assessment to be probably, possibly or definitely related to the MitraClip device.
 - Mitral valve stenosis
 - SLDA
 - Device Embolization
 - Iatrogenic atrial septal defect
 - Myocardial perforation
 - Need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device
- In-hospital MAE defined as the number of MAEs that occur prior to discharge from hospitalization in which MitraClip Procedure was performed
- MR Reduction to $\leq 1+$ at 30 days

4.3 Clinical Measures

(Discharge, 1, 6 and 12 months):

- All-cause Mortality
- Heart Failure Hospitalization
- MAE as defined above
- Device-Related Complications as defined above

4.4 Functional Improvement Measures

(Baseline, Discharge & 12 months)

- New York Heart Association (NYHA) functional class improvement
- Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)

4.5 Site Reported Echocardiographic Measures

(Baseline, Post Procedure, 1, & 12 months):

- MR Severity Grade
- Effective Regurgitant Orifice Area (EROA) as measured by measured by PISA method
- Coaptation Measures (depth/length)

- *Coaptation depth: Coaptation depth is defined as the distance from the plane of the mitral valve annulus to the first point of leaflet coaptation in the atrial-to-ventricular direction in the four-chamber view.*
- *Coaptation length: Coaptation length is defined as the vertical length of leaflets that is in contact, or is available for contact, during systole in the atrial-to-ventricular direction in the four-chamber view.*
- Flail Measures (gap/width)
 - *Flail Gap: Measured as the greatest distance between the ventricular side of the flail segment to the atrial side of the opposing leaflet. This distance is measured perpendicular to the plane of the annulus in two views and the largest measurement is used. The two views for measurement are the four-chamber long axis (LAX) view and the left ventricular outflow tract (LVOT) view.*
 - *Flail Width: Measured as the width of the leaflet segment that moves in and out of plane during systole in the short axis (SAX) view.*
- Grasping Area Anatomy (measure cleft or scallop if significant)
- Assess chordal support
- Regurgitant Jet(s) Position and Quantity
- TR Severity: None, Mild, Moderate or Severe

4.6 Core Lab Subgroup:

Subjects with evaluable echocardiograms may be selected for a more detailed assessment by an independent core lab. Pre-defined criteria will be used to identify eligible subjects for this assessment. A minimum of 100 subjects will be randomly selected from this eligible population.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This MitraClip® EXPAND Study will enroll male and female subjects with symptomatic mitral regurgitation who satisfy the inclusion and exclusion criteria and who are treated with the next generation MitraClip NTR System and/or MitraClip XTR System. The study will conduct analysis on approximately 1,000 subjects. Subjects must provide written informed consent prior to their data being submitted to the Study.

5.1.1 Anatomy Complexity

For analysis, subjects will be sorted into two groups based on valve anatomies identified to be important for MitraClip placement ^{26, 27, 28}

²⁶ Boerlage-van Dijk K, et al, Mitral valve anatomy predicts outcome of MitraClip implantation, *Int J Cardiol* (2014)

²⁷ Ambrožič J, Cvijič M, Bervar M, Bunc M., *Wien Klin Wochenschr*. Initial Slovenian experience with MitraClip therapy : Careful selection of patients is crucial for optimal outcome. 2017 Dec 4. doi: 10.1007/s00508-017-1295-7. [Epub ahead of print]

²⁸ Lesevic H, Karl M, Braun D, Barthel P, Orban M, Pache J, Hadamitzky M, Mehilli J, Stecher L, Massberg S, Ott I, Schunkert H, Kastrati A, Sonne C, Hausleiter J. Long-Term Outcomes after MitraClip Implantation According to the Presence or Absence of EVEREST Inclusion Criteria. *Am J Cardiol*. 2017; 119:1255-1261.

Group 1 (Complex Subjects):

If one or more of the following characteristics are present:

- Primary Jet outside of A2P2
- Presence of more than one significant jet
- Wide Jet
- Small Valve
- Calcified landing zone
- Minimal leaflet tissue for attachment (due to small coaptation length or too much coaptation depth)
- Presence of severely degenerative leaflets or wide flail gaps or widths

Group 2 (Non-Complex Subjects):

All subjects who do not qualify as a complex subject will be classified as Non-Complex subjects whose characteristics are similar to subjects enrolled in the EVEREST II trial.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

The hospital will follow their standard of care procedures for determining if a patient is eligible for treatment with a MitraClip® System. Consecutive MitraClip patients should be asked to provide consent for participation in the study if they are eligible per the inclusion/exclusion criteria (see section 5.2.3). Upon echocardiographic verification that there is no evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus per IFU requirements; the MitraClip procedure should be attempted. The procedure is considered attempted when the MitraClip delivery system is introduced. All consented patients with an attempted MitraClip procedure will be included in the study analysis.

5.2.2 Informed Consent

Patient Informed Consent Form must receive approval of Sponsor and EC/IRB prior to beginning enrollment into the MitraClip® EXPAND Study.

The Investigator or designee, who has been trained on the Protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subjects. For this study the subject will be treated per standard of care and must consent only to data collection (including echocardiogram) and follow-up visit schedule. All subjects (or legally authorized subjects' representatives if applicable) must sign, date and time (if required) the Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent prior to any clinical study-specific procedures. Obtaining the consent and provisioning of a copy to the subject, along with the date and time must be documented in the subject's medical records. In addition, the signed informed consent must be kept in the subject's medical records.

At sites in the United States, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally authorized representative. Per site requirements/preference HIPAA elements may be incorporated into the Informed Consent Form (ICF) or it may exist as a standalone document.

If approved by IRB/ EC, subjects from vulnerable populations may be enrolled in the study. ISO14155 definition of vulnerable population: Defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

5.3 Eligibility Criteria

Consecutive MitraClip patients should be screened per the criteria listed below. Assessment for eligibility criteria is based on medical records of the site and interview with a candidate subject. Subjects must meet ALL of the inclusion criteria to be considered for the clinical study. If ANY of the exclusion criteria are met, the subject is excluded from the clinical study. Consecutive patients meeting these criteria should be asked to provide consent for participation in the EXPAND Study.

5.3.1 Inclusion Criteria

1. Subjects who give consent for study participation
2. Subjects scheduled to receive the MitraClip per the current approved indications for use
3. Subjects with Symptomatic MR ($\geq 3+$)

5.3.2 Exclusion Criteria

1. Subjects participating in another clinical study that may impact the follow-up or results of this study.

5.4 Subject Enrollment and Inclusion

The patient is considered enrolled upon signing and dating an informed consent for participation. Consecutive enrolled patients with an attempted MitraClip procedure will be included in the analysis population.

5.5 Subject Discontinuation

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

- Subject death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically-indicated
- Subject lost-to follow-up as described below

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

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

Lost-to-Follow-up:

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

- A minimum of 2 telephone calls on different days over a 30-day period to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified if applicable) should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

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

5.6 Total Expected Duration of the Study

The time to complete the Study is estimated to be approximately 2 years.

5.7 Expected Duration of Each Subject's Participation

The expected duration of participation for subjects is approximately 12 months.

5.8 Number of Subjects Required to be Included in the Study

Approximately 1,000 subjects will be included for analysis in the Study.

5.9 Estimated Time Needed to Select this Number

The estimated time to include 1,000 analysis patients is about 1 year.

5.10 Study Completion

A Study Completion eCRF must be completed when:

- the subject is considered lost to follow-up per the above definition or
- the subject withdraws from the Study or
- the investigator withdraws the subject from the Study or
- the subject has died or

- upon Study completion (e.g., 1 year follow-up time point has been reached) or
- sponsor termination of Study

Sponsor must be notified of the reason for subject discontinuation. The site will provide this information on the electronic case report form (eCRF). Investigators must also report this to their EC/IRB as defined by their institution's procedure. Subjects will not be replaced.

6.0 TREATMENT AND FOLLOW-UP ASSESSMENTS

6.1 Pre-Treatment

Patients presenting with MR appropriate for treatment with the MitraClip® will undergo screening per standard hospital procedure in accordance with approved labelling. If a MitraClip procedure is considered appropriate (with agreement from local a heart team when required) and the patient meets the screening criteria for the study (i.e. Symptomatic MR \geq 3+ and not participating in another study) the site shall obtain consent from the patient. All efforts should be made by the site to obtain consent from consecutive eligible patients. Echocardiographic verification that there is no evidence of intracardiac, IVC or femoral venous thrombus is required prior to MitraClip procedure per the MitraClip IFU. The MitraClip procedure should be attempted for all consented patients with no evidence of thrombus.

6.1.1 Protocol Required Medications

All medication shall be administered per standard of care procedures for patients that undergo a MitraClip® procedure.

6.1.2 Clinical Assessments

Baseline assessment should be conducted per standard of care. Baseline information to be reported into the study include at minimum: medical history, age, weight, heart rate, blood pressure, history of heart failure hospitalizations, MR severity, and New York Heart Association (NYHA) Functional Class. A baseline QOL conducted by the KCCQ is required to be recorded and submitted for the study. If a 6-minute walk test is conducted as standard of care at baseline, these results will be collected in the EXPAND Study.

6.1.3 Pre-treatment Imaging

Pre-Treatment Transthoracic Echocardiogram (TTE) and Transesophageal Echocardiogram (TEE) should be conducted per standard of care for a MitraClip® Procedure. Copies of all Echocardiograms will be collected by the Sponsor for future reference and may be compared to follow-up echocardiograms.

6.2 Index Procedure

Please refer to IFU for instructions on handling and preparation of the MitraClip® System. All Investigators must read and understand the IFU that accompanies the Device.

6.2.1 Treatment

The MitraClip® procedure should be conducted in accordance with standard of care practice and approved labelling. All consecutive consented patients with an attempted MitraClip procedure will be entered into the study. A procedure is considered attempted when the MitraClip delivery system is introduced.

NOTE FOR U.S. Sites Only: In order to permit device reimbursement, please enter required data into the TVT Registry per your standard processes for all EXPAND Study cases. The data collected in this registry does not replace the data collected by the TVT Registry.

6.3 Post-Procedure

Post Clinical Assessments and Laboratory / Clinical Tests should be conducted per standard of care. Post-procedure information to be reported for this study include at minimum: adverse events, device performance, concurrent procedures, MR severity and NYHA Functional Class.

6.3.1 Final (Post-procedure) Imaging

Prior to discharge a TTE should be conducted per standard of care. The discharge TTE will be collected by the Sponsor for future reference and may be compared to baseline and/or follow-up TTEs.

6.4 Subject Follow-up

Follow-up is conducted per standard of care visits shown below. All follow-up assessment, visit or phone, should include a review for adverse events occurring since the last visit. Results from the KCCQ survey are required to be recorded and submitted at the 30-day and 12-month visits. Visit should be scheduled relative to the date of the MitraClip Procedure. If a 6-minute walk test is conducted as standard of and was conducted at baseline; results for 6-minute walk test at 30day and 12-months visits will be collected in the EXPAND Study.

Visits at:

- 30 days (30 days -14 days / +60 days)
- 12 months (365 days - 30 days / +90 days)

Phone call or visit at:

- 6 months (180 days - 30 days / +90 days)

6.4.1 Follow-Up Imaging

At the 30-day and 12-month follow-up visits a TTE should be conducted per standard of care. TTEs will be collected by the Sponsor for future reference and may be compared to baseline and/or follow-up TTEs.

During the follow-up period for this study (12 months) any unscheduled echocardiograms, either TEE or TTE, should be submitted to the Sponsor.

Table 2 outlines the assessment schedule for this study.

Table 2. Clinical Assessment Schedule

Required Assessments to be Collected	Pre-Treatment	Treatment	DIS	30-D	6-M	1-Y
				-14/+60 days	-30/+90 days	-30/+90 days
Informed Consent	X					
Medical History	X					
Medical Exam and Reporting of Vitals	X		X	X		X
NYHA Classification	X		X	X		X
KCCQ Survey	X			X		X
6 Minute Walk Test (Only if standard of care)	X			X		X
Adverse Events ¹		X	X	X	X	X
Transthoracic Echocardiography (TTE)	X	X ²	X	X		X
Transesophageal Echocardiography (TEE)	X	X ²				
Unscheduled Echocardiogram (TTE or TEE)			X	X	X	X

1. Adverse Events to be collected in this study include: cardiovascular events, device-related complications (as defined in section 4.2), and events classified as MAEs (as defined in section 4.1)
2. TTE and TEE during treatment should be submitted for the study only if capturing TTE and TTE echoes is part of standard of care.

7.0 ADVERSE EVENTS

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

7.1 Definitions

7.1.1 Adverse Event

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

Note 1: This definition includes events related to the device

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the MitraClip® 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 product, whether or not related to the medicinal product.

7.1.2 Serious Adverse Event

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

- a) Led to a death,
- b) Led to a serious deterioration in health 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.

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

7.1.3 Device Deficiency/Device Malfunction

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.

A device malfunction (DM) is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the IFU or protocol.

7.2 Device Relationship

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

7.3 Adverse Event/Device Deficiency/Product Experience Reporting

7.3.1 Adverse Event Reporting

The Investigator will monitor the occurrence of AEs for each subject during the course of the clinical study and report as required by this Protocol. AEs need to be collected on the appropriate AE eCRF form. Additional information with regards to an adverse event should be updated within the appropriate case report form.

Adverse Events to be reported during this study include: all cardiovascular events, device-related complications (as defined in section 4.2), and events classified as MAEs (as defined in section 4.1). These AEs should be reported starting from the time that the MitraClip delivery system is introduced to the femoral vein through the 12-month follow up visit in cases with a MitraClip implant. In cases with an attempted MitraClip Procedure, but no implant, AEs are only collected through 30 days post attempted procedure.

The investigator should report all required SAEs to the Sponsor as soon as possible but no later than 3 calendar days from the day the 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.

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

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the EDC system, however need to be reported via the Product Experience Report Form .

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

7.3.2 Device Deficiency/Device Malfunction Reporting

All device deficiencies/malfunctions should be reported within the Electronic Data Capture (EDC) System on the appropriate eCRF form no later than 3 calendar days from the day the 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.

A fax form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before *the patient ID has been assigned*, the device deficiency should be reported to the Sponsor via the Product Experience Report Form .

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

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

7.3.3 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

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

8.0 ADJUDICATION OF EVENTS

8.1 The Clinical Events Committee (CEC)

A Clinical Events Committee is comprised of qualified physicians who are not investigators in the study. The CEC will review and adjudicate pre-specified events reported by investigators or identified by the Safety & Surveillance personnel/designate for the study as documented in a CEC Manual of Operations (MOP).

9.0 STATISTICAL ANALYSIS

The following section describes the statistical methods for the clinical study. Details on statistical analyses are maintained in a separate Statistical Analysis Plan (SAP).

9.1 Statistical Overview

This is a post-market multicenter study of consecutive consenting patients have an attempted treatment with the MitraClip® NTR System and/or MitraClip® XTR System at participating centers. The study will include up to 1,000 subjects for analysis.

9.2 Analysis Populations

[REDACTED]

9.3 Sample Size Calculations and Assumptions

A sample size of 1000 subjects is expected to adequately capture data on a wide range of subjects with primary or secondary MR, subjects with or without complex valve anatomy, and subjects from Europe and the United States.

[REDACTED]

9.3.1 Planned Interim Analyses

There is no planned interim analysis to claim success of the study. Accumulating data from this study will be made public per the Publication Plan for the study.

9.4 Statistical Analyses

9.4.1 Endpoint Analysis

The intent of this study is to collect contemporary data in a real-world setting. All endpoints for this study will support a post-market assessment of device safety and performance. Descriptive analysis will be performed on the study data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in this section below will be used.

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

For binary variables such as APS, counts, percentages, and 95% confidence intervals based on Exact Clopper-Pearson method will be calculated.

For time to event data such as all-cause mortality, Kaplan-Meier analyses will be performed.

For recurrent event data such as recurrent heart failure hospitalizations at pre- and post-procedure, data will be analyzed using a generalized linear model, such as Poisson regression model.

Results from this study will be presented within the context of the literature on the MitraClip.

9.4.2 Subgroup Analysis

9.4.3 Handling of Multiplicity Issues

Details will be defined in the Statistical Analysis Plan (SAP).

9.4.4 Criteria for Early Termination of the Study for Efficacy

No formal statistical rule for early termination of the study is defined.

9.4.5 Procedures for Accounting for Missing, Unused or Spurious Data

All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate in the clinical report.

9.4.6 Pooling Strategy

Details on pooling strategy can be found in the SAP.

9.5 Deviations from the Original Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

10.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents in order for clinical study-related monitoring, audits, IRB/EC review and regulatory inspections to be performed.

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

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Selection of Clinical Sites and Investigators

Sponsor will select investigators qualified by training and experience, to participate in this MitraClip Post Market study. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the Principal Investigator or multidisciplinary team at the site.

11.2 Protocol Amendments

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

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.

11.3 Training

11.3.1 Site Training

All Investigators/study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators/study personnel will include, but is not limited to, the Protocol requirements, device usage, electronic case report form completion and study personnel responsibilities. All Investigators/study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigator/study personnel must not perform any study-related activities that are not considered standard of care at the site.

11.3.2 Training of Sponsor's Monitors

Sponsor and/or designated monitors will be trained to the Protocol, case report forms and device usage (as appropriate). Documentation of this training will be according to written procedures.

11.4 Monitoring

Per the Monitoring Plan, centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential CIP deviations that may be indicative of site non-compliance. On-site monitoring may occur at the discretion of the Sponsor.

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

The investigator understands and accepts the obligation to conduct the research study according to the Protocol and applicable regulations, and has signed the Investigator Agreement or the Clinical Study Agreement.

The Investigator and his/her staff have sufficient time and facilities to conduct the study and that they have access to an adequate number of appropriate subjects to conduct the study.

Source documentation (including original medical records) 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 case report forms, and device information.

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

11.5 Deviations from Protocol

The Investigator will not deviate from the Protocol for any reason without prior written approval from Sponsor except in cases of medical emergencies, when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing. All deviations must be reported to the Sponsor. In subject-specific deviations from the Protocol, a Protocol deviation case report form will be completed. The occurrence of Protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the Protocol and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all Protocol deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

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

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

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

11.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical study records, including source documentation, for inspection and duplication during a Quality Assurance audit. In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical study, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical study (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

11.7 Sponsor Auditing

In the event that an Investigator is contacted by a Regulatory Agency in relation to this clinical study, the Investigator will notify the Sponsor immediately and IRB/EC as appropriate. 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 study (e.g., Form FDA 483,

Inspectional Observations, and Warning Letters). The Sponsor may provide any needed assistance in responding to regulatory inspections.

11.8 Committees

11.8.1 Steering Committee

The Steering Committee will be led by two study Co-Primary Investigators (Co-PIs) whose names are specified on the cover page of this Protocol. In addition to the 2 Co-PIs, 8 key opinion leaders (whose names are also specified on the cover page of the protocol) will form the study Steering Committee. The Sponsor will be represented by at least one person each from the Clinical Science and Clinical Program Management groups. The Chairman of the core laboratories and other sponsor's personnel may also participate in the Committee meetings if appropriate. Meeting minutes from this committee will be filed with the sponsor.

The Steering Committee is responsible for overseeing the scientific and operational aspects of the study. This committee will meet regularly to monitor study progress, general data collection and non-compliance with the study protocol at individual centers, to review operational issues that may arise and warrant a Protocol amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the study.

11.8.2 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the study. The CEC will review and adjudicate events as defined in the CEC charter and according to definitions provided in this Protocol.

12.0 DATA HANDLING AND RECORD KEEPING

Data Management will include documentation of the systems and procedures used in data collection for the duration of the study.

All CRF 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. Passwords and electronic signatures will be strictly confidential.

All CRF data will be downloaded from the EDC system and reformatted into a data structure acceptable to Abbott. The data will be subjected to consistency and validation checks within the EDC system and will be subject to supplemental validation following download.

At the conclusion of the study, completed Case Report Form (CRF) images 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 for each site and a backup copy archived with Abbott.

For the clinical study duration, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical study progress records, laboratory reports, electronic case report forms, signed ICFs, device accountability records, correspondence with the

IRB/EC and clinical study monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical study.

12.1 Source Documentation

Regulations and Good Clinical Practice (GCP) require that the Investigator maintain information in the subject's original medical records that corroborates data collected on the case report forms. 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 study:

- Medical history/physical condition of the subject before involvement in the study sufficient to verify Protocol entry criteria
- Dated and signed notes on the day of entry into the study referencing the Sponsor, Protocol number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution including supporting documents such as discharge summaries, catheterization laboratory reports, Electrocardiograms (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, reviewed and annotated for clinical significance of out of range results. *Note: With electronic medical records some clinical sites may be able to annotate that labs or ECG have been reviewed in the system. For those sites that do not have such capability the labs or ECG may be able to be printed or signed. Each study team should include protocol language regarding these processes that is most suitable for the specific study.*
- Notes regarding Protocol-required and prescription medications taken during the study (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the study
- Any other data required to substantiate data entered into the CRF

12.2 Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the Protocol and eCRF completion. eCRF data will be collected for all patients in the study.

12.3 Record Retention

The Sponsor will archive and retain all documents pertaining to the study 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 study records.

13.0 ETHICAL CONSIDERATION

13.1 Institutional Review Board/Medical Ethics Committee Review

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the Protocol, ICF and other written information provided to the patient will be obtained by the Principal Investigator at each prior to participation in this clinical study. The approval letter must be received prior to the start of this

clinical study and a copy must be provided to the Sponsor. No changes will be made to the Protocol or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and/or the regulatory agencies.

Until the clinical study is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical study, per IRB/EC requirements. Ongoing written approval will be obtained from the IRB/EC according to each institution's IRB/EC requirements. Further, any amendments to the Protocol as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

14.0 PUBLICATION POLICY

The data and results from the study are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical study. The Investigators will not use the Clinical study-related data without the written consent of the Sponsor for any other purpose than for Clinical study completion or for generation of publication material, as referenced in the Clinical Study Site Agreement. The publication and/or presentation of results from a single clinical study site are not allowed until publication and/or presentation of the multi-center results. The Sponsor acknowledges that the study's Principal Investigator intends to publish a multi-center publication regarding the clinical study results. The Sponsor must receive any proposed publication and/or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the Clinical Study Site Agreement.

The Sponsor will be responsible for determining whether to register the Clinical study on www.clinicaltrials.gov or any other clinical study registration sites, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the Study should be registered, Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Institution and/or Principal Investigator(s) shall not take any action to register the study.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

The new MitraClip NTR System is a modification to the DC of the MitraClip NT System and is intended to make the procedure easier, more precise, more predictable, and to optimize manufacturability of the product. The MitraClip XTR System, which includes the same modified DC and longer clip arms on the implant, was designed for grasping mitral leaflets. Based on testing, grasping leaflets with MitraClip XTR will be easier in certain patients. In design validation testing, differentiation of ease of grasping between MitraClip NT and MitraClip XTR Systems was found in a model which simulated a mixed functional/degenerative etiology procedure with a tethered posterior leaflet and a flailing anterior leaflet. The end result of both grasping procedures were successful as both MitraClip NT System and MitraClip XTR System were able to successfully grasp the coapt leaflets however the user was able to perform the steps in less attempts with MitraClip XTR. In other development tests prior to the design validation, both the MitraClip NT and MitraClip XTR devices were able to grasp leaflets equivalently. Subjects with such anatomies may therefore benefit from treatment with the MitraClip XTR. Moreover, the improved DC may simplify the MitraClip procedure compared to the

current iteration of the MitraClip System. Data from this study may help to elucidate this and to further identify the anatomical characteristics that can be treated with the MitraClip NTR or the MitraClip XTR device.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Per the MitraClip IFU, The ANTICIPATED EVENTS on **Table 3** have been identified as possible.

Table 3. Potential Complications and Adverse Events (from MitraClip® IFU)

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

15.3 Residual Risks Associated with the Investigational Device

This is a post-market study on an approved commercial device. There is no investigational device being used as part of this study.

15.4 Risks Associated with Participation in Clinical Study

Treatment with the MitraClip® device as part of this study is identical to treatment with the MitraClip® device outside of this study. Participation in the study will not impact the MitraClip procedure or use of the MitraClip in any way. Participation in the study requires submission of data that may or may not be protected health information. This information should be kept confidential, but there is a risk that some of the information could be unintentionally made non-confidential. The risk of this happening for this study is no greater than the risk of loss of confidentiality in any study.

15.5 Possible Interactions with Protocol-Required Concomitant Medications

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

15.6 Steps that will be Taken to Control or Mitigate the Risks

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

Risks associated with the use of the device during this clinical study are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the protocol. All adverse events and device deficiencies will be reported to Abbott and will be monitored internally for safety surveillance purposes.

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

15.7 Risk to Benefit Rationale

Subjects participating in this study will be receiving the latest technology in MitraClip which has been shown to be safe and effective in over 4,500 patients in clinical trials and more than 50,000 patients in worldwide use to date. This is a post-market study being conducted on an approved device within the standard of care procedures. The risks associated with receiving a MitraClip implant within this study are identical to the risks of receiving a MitraClip implant outside of the study.

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

APPENDIX I: MITRACLIP XTR PMCF CLINICAL STUDY PROTOCOL

Defines a statistical analysis to be conducted for the first 220 European Patients in the EXPAND Study treated with the MitraClip XTR System

**17-518-1: MitraClip XTR PMCF Study****A Post-Market Clinical Follow-up Assessment of the Safety and Performance the MitraClip XTR System**


Version Number	2.0
Date	26 June 2018
Planned Number of Sites and Region(s)	Up to 50 sites in Europe
Protocol Author	 Senior Principal Clinical Research Scientist Abbott Structural Heart

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COMPLIANCE STATEMENT:

This study will be conducted in accordance with this Plan, the Declaration of Helsinki, applicable Good Clinical Practices and applicable regulations including ISO14155 and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the study will be approved by the appropriate Institutional Ethics Committee (EC) of the respective study site and by the applicable regulatory authorities.

PROTOCOL SUMMARY

Protocol Name and Number	17-518-1: MitraClip XTR PMCF Study
Title	Post-Market Clinical Follow-up Assessment of the Safety and Performance the MitraClip XTR System
Objectives	The primary objective of this study to evaluate the safety and performance of the MitraClip XTR System in a post-market setting.
Device	MitraClip XTR System
Targeted number of subjects	A minimum of 220 subjects
Subject Follow-up	Clinical Visit: 30 days and 12 Months Phone Call: 6 Months
Primary Endpoint	<u>Safety and Effectiveness</u> Acute Procedural Success (APS) defined as successful implantation of the MitraClip XTR device with resulting MR severity of 2+ or less on discharge Echocardiogram (30-day echocardiogram will be used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are considered to be an APS failure
Clinical Endpoints	<ul style="list-style-type: none"> • Major Adverse Event (MAE). MAE defined as a composite of all-cause Death, Myocardial Infarction, Stroke, or non-elective CV surgery for device related complications (CEC adjudicated) • MR Severity • Device Related Adverse Events (including Mitral valve stenosis, device embolization, Single Leaflet Device Attachment (SLDA), iatrogenic atrial septal defect, Myocardial perforation, 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)) • All-cause mortality • Recurrent heart failure hospitalization • New York Heart Association (NYHA) functional class improvement
Inclusion Criteria	<ol style="list-style-type: none"> 1. Subjects scheduled to receive the MitraClip per the current approved indications for use 2. Subjects who give consent for their participation 3. Subjects with Symptomatic MR ($\geq 3+$)
Exclusion Criteria	<ol style="list-style-type: none"> 1. Subjects participating in another clinical study that could impact the follow-up or results of this study.

1.0 INTRODUCTION

This clinical study protocol defines the MitraClip XTR PMCF study being conducted to confirm the safety and performance of the MitraClip XTR in a post-market setting. The MitraClip XTR System introduces a new delivery catheter design intended to make procedure easier, more precise, more predictable, and to optimize manufacturability and an additional implant size intended to assist clinicians with leaflet grasping. Although there is extensive published clinical evidence on the safety and performance of the MitraClip system (see section 2.1), the safety and performance of the MitraClip XTR system has not yet been evaluated in a clinical study.

This PMCF study will be conducted on commercial MitraClip XTR devices that have received CE Mark and will be used to fulfill the regulatory requirement for post-market clinical follow-up (PMCF).

1.1 Study Design

This is a Post-Market, Multi-Center, International, Single-Arm, Prospective Study to assess the safety and performance of the next generation MitraClip XTR System by comparing the rate of acute procedural success after treatment with the MitraClip XTR to an expected rate based on historical MitraClip data.

A minimum of 220 post-market, consecutive, consented, patients treated with the MitraClip XTR device in the EU will be included for analysis into the MitraClip XTR PMCF study. Clinical follow-up visits will be requested at 30 days and at 12 months post-procedure with an additional clinical follow-up phone call at 6 months. Reported adverse events through 12 months will be assessed to further confirm safety.

1.2 Study Objective

The primary objective of this study is to assess the safety and performance of the MitraClip XTR System in a post-market setting. This study will be conducted in accordance with post market clinical follow-up requirements.

2.0 BACKGROUND INFORMATION

2.1 Literature Review

The MitraClip System received approval for commercialization in Europe in March 2008, and is indicated for reconstruction of the insufficient mitral valve through tissue approximation. Since approval, there have been a number of commercial studies in Europe on the MitraClip.

ACCESS-EU²⁹ was a two-phase prospective, single-arm, multicenter post-approval observational study of the MitraClip in Europe for the treatment of MR. The primary objective was to gain information with respect to health economics and clinical care, and to provide further evidence of safety and effectiveness. Five hundred sixty-seven (567) patients were treated with the MitraClip. One-year clinical follow-up was available in 487 patients. Considering the high MitraClip device implant rate (99.6%, 565/567), the high rate of meaningful MR reduction (78.9%, 258/327 MR<2+), and the resulting improvements in 6-minute

²⁹ Maisano F, Franzen O, Baldus S, Schafer 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 1-Year Results from the ACCESS-EU, a Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe. *J Am Coll Cardiol*. 2013; 62:1052-1061.

walk (59.5 m difference, $p < 0.0001$), Minnesota Living with Heart Failure Questionnaire quality of life score (13.5 point improvement, $p < 0.0001$) and NYHA Functional Class (71.5% NYHA Class I or II, $p < 0.0001$), at 1 year, the study is concluded that the MitraClip device provides an important therapeutic option for patients with significant mitral regurgitation, and is an especially important option for patients who may be considered high surgical risk.

The GRASP registry was a single-center, prospective, observational study of consecutive high surgical risk patients with moderate-to-severe or severe MR undergoing percutaneous mitral valve repair with the MitraClip System at Ferrarotto Hospital (Catania, Italy). The study does not have specific exclusion criteria; and the indication for MitraClip therapy was established by a multidisciplinary Heart Team. The degree of preprocedural MR was quantified according to current guidelines by two expert echocardiographers. A total of 117 consecutive patients underwent MitraClip implantation between August 2008 and October 2012 as part of the GRASP registry³⁰. MR grade 3+ or 4+ was present in 98% of patients, and NYHA functional class symptoms in 80% of patients. Acute procedural success was achieved in all patients. MR was reduced to 1+ and 2+ post-procedure in 63% and 37% of patients, respectively. MAEs occurred in 4 patients (4.3%) at 30 days. One patient died from gastrointestinal bleeding within 30 days. Results from the GRASP registry further support the safety and efficacy of the MitraClip device in a real-world setting.

The German transcatheter mitral valve interventions (TRAMI) registry was initiated in August 2010 to collect data from clinical centers in Germany involved in transcatheter therapies for mitral valve disease. The registry comprises a retrospective part, including patients who have been treated at individual sites prior to study initiation, and a prospective part after study site initiation. Follow-up for the retrospective part was not defined in the study protocol and was performed according to institutional practice. Follow-up for the prospective part was scheduled at 30 days and then at 1, 3, and 5 years. Several reports on TRAMI have been published over the years^{31,32}. The largest prospective cohort was described by Puls et al.³³. A total of 828 patients were prospectively enrolled at 21 German sites between 2010 and 2013. One-year follow-up was available in 749 patients. The MitraClip implant rate in this cohort was 97%, with an average of 1.4 ± 0.6 clips implanted per procedure. Mitral regurgitation was reduced from severe (94%) at baseline to none or mild in 85.2% of patients post procedure. One patient died intra-operatively and in-hospital mortality was 2.4% ($n=18$). No emergent cardiac surgery was required. The rate of in-hospital Major adverse cardiac and cerebrovascular events (MACCE) was 3.1%. These results demonstrate that treatment of significant MR with the MitraClip device is efficacious and results in

³⁰ Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistrutto A, Ministeri M, Barbanti M, Caggegi A, Chiaranda M, Dipasqua F, Giaquinta S, Occhipinti M, Ussia G, Tamburino C. One- and Twelve-Month Safety and Efficacy Outcomes of Patients Undergoing Edge-to-Edge Percutaneous Mitral Valve Repair (from the GRASP Registry). *Am J Cardiol.* 2013; 111:1482-1487.

³¹ Baldus S, Schillinger W, Franzen O, Bekeredjian R, Sievert H, Schofer J, Kuck KH, Konorza T, Mollmann H, Hehrlein C, Ouarrak T, Senges J, Meinertz T, investigators GTMVI. MitraClip Therapy in Daily Clinical Practice: Initial Results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. *Eur J Heart Fail.* 2012; 14:1050-1055.

³² Schillinger W, Hunlich M, Baldus S, Ouarrak T, Boekstegers P, Hink U, Butter C, Bekeredjian R, Plicht B, Sievert H, Schofer J, Senges J, Meinertz T, Hasenfuss G. Acute Outcomes after MitraClip Therapy in Highly Aged Patients: Results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. *EuroIntervention.* 2013; 9:84-90.

³³ Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-Year Outcomes and Predictors of Mortality after MitraClip Therapy in Contemporary Clinical Practice: Results from the German Transcatheter Mitral Valve Interventions Registry. *Eur Heart J.* 2016; 37:703-712.

significant clinical improvements in a high proportion of TRAMI patients after 12 months. In this cohort, failure to achieve procedural success had the highest hazard ratio for predicting 1-year mortality.

The Transcatheter Valve Treatment Sentinel Pilot Registry is part of the European Society of Cardiology EuroObservational Research Programme and reports acute and 12-month follow-up results of 628 consecutive patients treated between January 2011 and December 2012 in 25 centers in 8 European countries. Acute procedural success was high (95.4%) with no difference between FMR and DMR patients. Overall, in-hospital mortality was 2.9%. MR reduction to $\leq 2+$ was achieved in 98.2% of patients post-procedure with no difference between MR etiologies. At 1-year, MR was reduced to $\leq 2+$ in 94.0% of patients and 58.6% had mild or no MR, with comparable results obtained for FMR and DMR. The results of the pilot European Sentinel Registry demonstrated that procedural and late mortality was low and lower than expected in such a high-risk cohort, without differences between FMR and DMR. These results confirm long-term benefits previously reported in other real-world registries.

The totality of post-market clinical evidence supports the use of the MitraClip System for the treatment of MR. The MitraClip XTR PMCF Study will assess the safety and performance of the next generation MitraClip XTR system to confirm that the new design also performs safely and with acceptable outcomes.

2.2 Rationale for Conducting this Study

This Study will meet PMCF requirements to confirm safety and performance of the next generation MitraClip XTR System. The primary analysis will be conducted using the endpoint of Acute Procedural Success (APS). APS is evaluated by taking into account both safety and performance by capturing safety events related to device failure (re-intervention or death) and performance by the assessment of MR (reduced MR to MR $2+$ or less). APS will be evaluated upon discharge from the hospital post procedure. A comparison to the APS rate established by historical clinical data will show the next generation MitraClip XTR System offers the safety and performance expected from MitraClip.

2.3 Summary of Device

2.3.1 Name of the Device

Patients will be treated with MitraClip XTR System as part of this study after all required commercial approval for the device is obtained.

2.3.2 Indication for Use

MitraClip XTR procedures for this study will be conducted in accordance with the Instructions for Use (IFU) that is approved for the region, where the implant is taking place.

2.3.3 Description of the Device

The MitraClip System is intended for reconstruction of the insufficient mitral valve through tissue approximation. The MitraClip System comprises of the Clip Delivery System and Steerable Guide Catheter. The Clip Delivery System is introduced into the body through the Steerable Guide Catheter.

The MitraClip XTR System is an additional implant size to be used with a modified Delivery Catheter. The additional implant size is intended to assist clinicians with leaflet grasping. The modified delivery catheter is designed to make the procedure more precise, more predictable, and to optimize manufacturability of the product.

3.0 FOLLOW-UP SCHEDULE

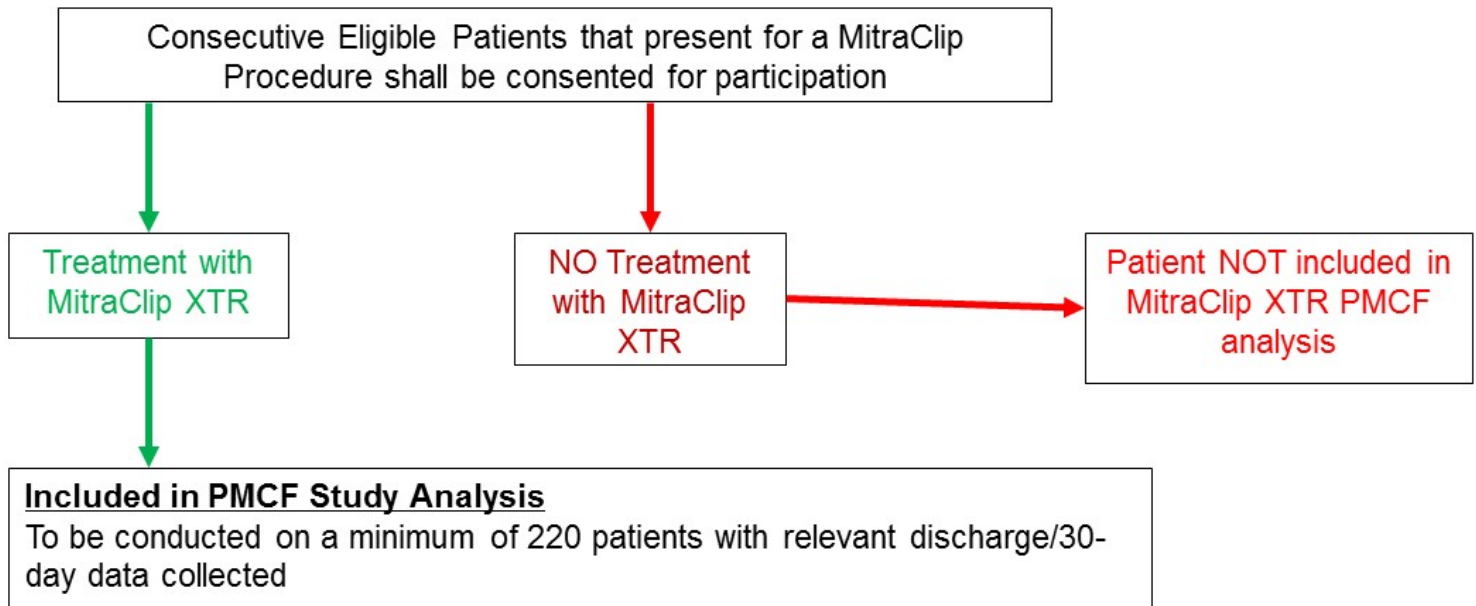
3.1 Number of Subjects to be Enrolled

Subjects who have provided written informed consent are considered enrolled. Upon treatment with MitraClip XTR the subject will be included in this PMCF analysis. A minimum of 220 commercial MitraClip XTR patients will be analyzed at a maximum of 50 centers in the EU as part of this PMCF study.

3.2 Overall Flow of the Study and Follow-up Schedule

Consecutive eligible patients that present for MitraClip procedure should be consented for the MitraClip XTR PMCF Study. Patients are included in the analysis upon completion of MitraClip XTR procedure. A schematic of the study flow for the study is shown in **Figure 1**.

Figure 1: Schematic for Study Inclusion



3.3 Early Termination of the Clinical Study

No formal statistical rule for early termination of the MitraClip XTR PMCF Study is defined. The Sponsor reserves the right to discontinue the study at any stage or reduce the follow up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (UADE) occurs and it presents an unreasonable risk to the participating subjects.
- Further product development is cancelled.

Should the study be discontinued by the Sponsor, patients will be followed up as per routine hospital practice with device related AEs being reported to the Sponsor as per vigilance/commercial reporting requirements. Should this occur, the investigator shall return all clinical study materials to the Sponsor, and provide a written statement as to why the premature termination has taken place to the EC.

4.0 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is Acute Procedural Success (APS). This is defined as successful implantation of the MitraClip device with resulting MR severity of 2+ or less upon discharge Echocardiogram (30-day echocardiogram will be used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are an APS failure

4.2 Clinical Endpoints

Clinical Endpoints will be assessed at each study time point, all data reported at the corresponding study visit will be included for the study time point.

- Major Adverse Events (MAE): defined as a composite of CEC adjudicated all-cause Death, Myocardial Infarction, Stroke, or non-elective CV surgery for device related complications
- MR Severity
- Device Related Adverse Events (including mitral valve stenosis, device embolization, single leaflet device attachment (SLDA), iatrogenic atrial septal defect, myocardial perforation, 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)
- All-cause mortality
- Recurrent heart failure hospitalization
- New York Heart Association (NYHA) functional class improvement

4.3 Success Criteria

The MitraClip XTR PMCF Study will be successful if the lower one-sided 95% confidence interval (CI) of the observed APS rate for the study is greater than the Performance Goal (PG) of 80.7%.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This study will include an analysis of male and female consented subjects from the heart failure population who satisfy the inclusion and exclusion criteria and who are treated with the MitraClip XTR System. The study will include a minimum of 220 subjects.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

The hospital will follow their standard of care procedures for determining if a patient is eligible for treatment with a MitraClip System. Consecutive patients who present for their procedure should be asked to provide consent for participation in the MitraClip XTR PMCF Study if they are eligible per the inclusion/exclusion criteria. Only patients that have a MitraClip XTR implanted will be included in the analysis.

5.2.2 Informed Consent

Patient Information and Consent Form must receive approval of Sponsor and EC/IRB prior to beginning enrollment into the MitraClip XTR PMCF Study

The Investigator or designee, who has been trained on the Study, will explain the nature and scope, potential risks and benefits of participation, and answer questions for the subjects. The subject will be treated with the MitraClip System per standard of care and must consent only to data collection and follow-up visit schedule. All subjects (or legally authorized subjects' representatives if applicable) must sign, date and time (if required) the Ethics Committee (EC) approved informed consent prior to any data is reported into the PMCF study. Obtaining the consent and provisioning of a copy to the subject, must be documented in the subject's medical records. In addition, the signed informed consent must be kept in the subject's medical records.

If approved by the EC, subjects from vulnerable populations may be enrolled in the study. ISO14155 definition of vulnerable population: Defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

5.3 Eligibility Criteria

Consented subjects treated commercially with the MitraClip XTR System will be considered. All subjects must meet the criteria below before being included in the MitraClip XTR Study.

5.3.1 Inclusion Criteria

1. Subjects scheduled to receive the MitraClip per the current approved indications for use
2. Subjects who give consent for their participation
3. Subjects with Symptomatic MR ($\geq 3+$)

5.3.2 Exclusion Criteria

1. Subjects participating in another clinical study that could impact the follow-up or results of this study.

5.4 Subject Enrollment and Inclusion in Analysis

The patient is considered enrolled upon signing and dating an informed consent for participation. Only subjects that have an MitraClip XTR implant will be included in the analysis.

5.5 Total Expected Duration of the Study

The time to complete the MitraClip XTR PMCF Study is estimated to be approximately 18 months.

5.6 Expected Duration of Each Subject's Participation

The final required visit for subjects in the MitraClip XTR PMCF Study is at 12 months post-procedure. Therefore, the expected duration of participation for subjects is approximately 12 months.

5.7 Number of Subjects Required to be Included in the Study

A minimum of 220 subjects will be included in the MitraClip XTR PMCF Study

5.8 Estimated Time Needed to Select this Number

The estimated time to include 220 patients is about 6 months.

5.9 Subject Discontinuation

Subjects that are consented and receive a MitraClip XTR implant shall remain in the study until completion of the required follow-up period; however, a subject's participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically-indicated
- Subject lost-to follow-up as described below

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective EC as defined by their institution's procedure(s). No additional follow-up will be required or data recorded from subjects once withdrawn, except for the status (deceased/alive). However, if a subject withdraws due to problems related to the device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Lost-to-Follow-up:

If the subject misses two consecutive scheduled follow up time points and the attempts at contacting the subject 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.

6.0 TREATMENT AND EVALUATION OF SAFETY AND EFFICACY

6.1 Pre-treatment

Patients presenting with MR appropriate for treatment with the MitraClip will undergo screening per standard hospital procedure. If a MitraClip procedure is considered appropriate and the patient meets the screening criteria for the study (i.e. MR>3+, compliance with MitraClip approved labelling, and not participating in another study) the site shall obtain consent from the patient. The consent will permit information about the patient to be submitted to the study after successful implantation of MitraClip XTR device. No data may be entered into the study unless the informed consent is completed.

6.1.1 Clinical Assessments

Upon completion of Informed Consent, baseline assessment should be conducted per standard of care. Baseline information to be reported into the study include at minimum: medical history, weight, heart rate, blood pressure, MR severity and New York Heart Association (NYHA) Functional Class.

6.1.2 Pre-treatment Imaging

Pre-Treatment TTE and TEE should be conducted per standard of care for a MitraClip Procedure.

6.2 Index Procedure

Please refer to Instructions for Use (IFU) for instructions on handling and preparation of the XTR MitraClip System. All Investigators must read and understand the Instructions for Use (IFU) that accompanies the Device.

6.2.1 Treatment Strategy or Treatment Procedures

The MitraClip procedure should be conducted in accordance with standard of care practice and approved labelling. All consented patients that have the MitraClip XTR implanted will be entered into the study.

6.3 Post-procedure

Post treatment TTEs/TEES, Clinical Assessments and Laboratory / Clinical Tests should be conducted per standard of care. Post-procedure information to be reported for this study include at minimum: adverse events, MR severity and New York Heart Association (NYHA) Functional Class.

6.4 Subject Follow-up

Follow-up is conducted per standard of care at 30 days and 12 months post-procedure. A 6-month phone call is requested for patients in the study to assess for new adverse event. **Table 1** below outlines the follow-up schedule for this study.

Table1. Clinical Follow-Up Schedule

Required Assessments	Pre-Treatment	DIS	30-D	6-M	1-Y
			-14/+60 days	-30/+9 days	-30/+9 days
Informed Consent	X				
Medical history	X				
Medical Exam and Reporting of Vitals	X	X	X		X
NYHA Classification	X	X	X		X
Adverse events and hospitalizations ¹	X	X	X	X	X

¹. Adverse Events to be collected in this study include: all cardiovascular events, device-related complications (as defined in section 4.2), and events classified as MAEs (as defined in section 4.2)

7.0 Adverse Events

7.1 Definitions

7.1.1 Adverse Event

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

Note 1: This definition includes events related to the device

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the MitraClip 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 product, whether or not related to the medicinal product.

7.1.2 Serious Adverse Event

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

- a) Led to a death,
- b) Led to a serious deterioration in health 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.

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

7.1.3 Device Deficiency/Device Malfunction

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.

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

7.2 Device Relationship

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

7.3 Adverse Event/Device Deficiency/Product Experience Reporting

7.3.1 Adverse Event Reporting

The Investigator will monitor the occurrence of AEs for each subject during the course of the clinical study and report as required by this Protocol in section 7 per AE and SAE definitions. Adverse Events to reported during this study include: all cardiovascular events, device-related complications (as defined in section 4.2), and events classified as MAEs (as defined in section 4.2). These AEs should be reported starting from the time that the MitraClip delivery system is introduced to the femoral vein through the 12-month follow up visit.

The investigator should report all required SAEs to the Sponsor as soon as possible but no later than 3 calendar days from the day the 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.

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

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

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

7.3.2 Device Deficiency/Device Malfunction Reporting

All device deficiencies/malfunctions should be reported within the EDC System on the appropriate eCRF form no later than 3 calendar days from the day the 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 device, if not implanted or not remaining in the subject, should be returned to Abbott.

Device deficiencies/malfunctions should be reported to the EC per the investigative site's local requirements. A fax form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

7.3.3 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report the SAEs and Device Deficiencies to the country regulatory authority, per local and regional requirements.

8.0 ADJUDICATION OF EVENTS

8.1 The Clinical Events Committee (CEC)

The Clinical Events Committee is comprised of qualified physicians who are not investigators in the study. The CEC will review and adjudicate pre-specified events reported by study investigators or identified by the Safety & Surveillance for the study as documented in CEC Manual of Operations (MOPs).

9.0 STATISTICAL ANALYSIS

9.1 Statistical Overview

This is a post-market multicenter study of consecutive consenting patients treated with the MitraClip XTR system at participating centers. The study will enroll a minimum of 220 subjects to collect clinical evidence for the MitraClip XTR system to characterize the use and outcomes associated with the device. The primary endpoint is Acute Procedural Success (APS). APS is defined as successful implantation of the MitraClip Implant with resulting MR severity of 2+ or less on discharge Echocardiogram (30-day echocardiogram will be used if discharge information is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are considered as an APS failure.

9.2 Analysis Populations

9.3 Sample Size Calculations and Assumptions

The sample size of a minimum 220 subjects is determined based on the endpoint of APS. APS is defined as successful implantation of the MitraClip Implant with resulting MR severity of 2+ or less on discharge Echocardiogram.

The powered endpoint of APS will be evaluated against a pre-specified clinical performance goal (PG). The power calculation is based on the following statistical hypotheses and assumptions:

- H₀: APS rate ≤ PG
- H_A: APS rate > PG

- [REDACTED]
- One-sided type I error rate = 0.05

[REDACTED]

[REDACTED]

The sample size calculation was performed using PASS 15 (Hintze J, 2017, NCSS, LLC. Kaysville, Utah).

9.4 Statistical Analyses

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

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

For binary variables such as APS, counts, percentages, and 95% confidence intervals based on Exact Clopper-Pearson method will be calculated, and p-values may be presented for hypothesis generating purposes.

For time to event data such as all-cause mortality, Kaplan-Meier analyses will be performed.

For recurrent event data such as recurrent heart failure hospitalizations at pre- and post-procedure, data will be analyzed using a generalized linear model, such as Poisson regression model. A p-value to measure the strength of evidence may be provided for descriptive purposes.

9.4.1 Primary Endpoint Analysis

The exact test against PG will be performed for the primary endpoint in the analysis population. The null and alternative hypotheses will be of the following form:

H_0 : APS rate \leq PG

H_A : APS rate $>$ PG

APS is the Acute Procedural Success.

[REDACTED]

[REDACTED]

[REDACTED]



9.4.2 Clinical Endpoint Analyses

Clinical endpoints defined in section 4.0 will be summarized descriptively using methods described in Section 9.4.

9.4.3 Handling of Multiplicity Issues

There is a single primary endpoint and hence no multiplicity adjustment is needed.

9.4.4 Procedures for Accounting for Missing, Unused or Spurious Data

If Echocardiography assessed MR severity at discharge is unavailable or cannot be assessed, the 30-day value will be used to assess APS. All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate

9.5 Deviations from the Original Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

10.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents in order for clinical study-related monitoring, audits, EC review and regulatory inspections to be performed.

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

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Selection of Clinical Sites and Investigators

Sponsor will select investigators qualified by training and experience, to participate in the study of the MitraClip XR device. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the Principal Investigator or multidisciplinary team at the site.

11.2 Protocol Amendments

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

Acknowledgement/approval by the 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.

11.3 Training

11.3.1 Site Training

All study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of study personnel will include, but is not limited to, the Protocol requirements, device usage, electronic case report form completion and study personnel responsibilities. All study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigator/study personnel must not perform any study-related activities that are not considered standard of care at the site.

11.3.2 Training of Sponsor's Monitors

Sponsor and/or designated monitors will be trained to the Protocol, case report forms and device usage (as appropriate). Documentation of this training will be according to written procedures.

11.4 Monitoring

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

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

- The investigator understands and accepts the obligation to conduct the research study according to the Protocol and applicable regulations, and has signed the Investigator Agreement or the Clinical Study Agreement.
- The Investigator and his/her staff have sufficient time and facilities to conduct the study and that they have access to an adequate number of appropriate subjects to conduct the study.
- Source documentation (including original medical records) 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 case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

11.5 Deviations from Protocol

The Investigator will not deviate from the Protocol for any reason without prior written approval from Sponsor except in cases of medical emergencies, when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing. All deviations must be reported to the Sponsor.

11.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical study records, including source documentation, for inspection and duplication during a Quality Assurance audit. In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical study, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical study. Sponsor may provide any needed assistance in responding to regulatory audits.

11.7 Sponsor Auditing

In the event that an Investigator is contacted by a Regulatory Agency in relation to this clinical study, the Investigator will notify the Sponsor immediately and EC as appropriate. 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 study. The Sponsor may provide any needed assistance in responding to regulatory inspections.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data Management/Data Analysis

Data Management will include documentation of the systems and procedures used in data collection for the duration of the study. All CRF 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. Passwords and electronic signatures will be strictly confidential.

All CRF data will be downloaded from the EDC system and reformatted into a data structure acceptable to Abbott. The data will be subjected to consistency and validation checks within the EDC system and will be subject to supplemental validation following download.

At the conclusion of the study, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived for each study site and a backup copy archived with Abbott.

For the clinical study duration, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical study progress records, laboratory reports, electronic case report forms, signed ICFs, device accountability records, correspondence with the

IRB/EC and clinical study monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical study.

12.2 Source Documentation

Regulations and GCP require that the Investigator maintain information in the subject's original medical records that corroborates data collected on the case report forms. 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 study:

- Medical history/physical condition of the subject before involvement in the study sufficient to verify Protocol entry criteria
- Dated and signed notes on the day of entry into the study referencing the Sponsor, Protocol number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution including supporting documents such as discharge summaries and lab results including documentation of site awareness of SAEs and of investigator device relationship assessment of SAEs.
- Subject's condition upon completion of or withdrawal from the study
- Any other data required to substantiate data entered into the CRF

12.3 Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the Protocol and eCRF completion. eCRF data will be collected for all patients in the study.

12.4 Record Retention

The Sponsor will archive and retain all documents pertaining to the study 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 study records.

13.0 ETHICAL CONSIDERATION

13.1 Medical Ethics Committee Review

Ethics Committee (EC) approval for the Protocol and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each study site prior to participation in this clinical study. The approval letter must be received prior to the start of this clinical study and a copy must be provided to the Sponsor. No changes will be made to the Protocol or ICF or other written information provided to the patient without appropriate approvals, including EC, the Sponsor, and/or the regulatory agencies as needed.

Until the clinical study is completed, the Investigator will advise his/her EC of the progress of this clinical study, per EC requirements.

14.0 RISK ANALYSIS

14.1 Anticipated Clinical Benefits

The MitraClip XTR was designed for grasping mitral leaflets. Based on testing, grasping leaflets with XTR will be easier in certain patients. In design validation testing, differentiation of ease of grasping between NT and XTR was found in a model which simulated a mixed functional/degenerative etiology procedure with a tethered posterior leaflet and a flailing anterior leaflet. The end result of both grasping procedures were successful as both NT and XTR were able to successfully grasp and coapt leaflets however the user was able to perform the steps in less attempts with XTR. In other development tests prior to the design validation, both the NT and XTR devices were able to grasp leaflets equivalently. Subjects with such anatomies may therefore benefit from treatment with the MitraClip XTR. Data from this study may help to further identify the anatomical characteristics that can be treated with the MitraClip XTR device.

14.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Per the device IFU, the ANTICIPATED EVENTS on the table below have been identified as possible complications of the MitraClip procedure.

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

This is a post-market study on an approved commercial device. There is no investigational device being used as part of this study.

14.4 Risks Associated with Participation in Clinical Study

Treatment with the MitraClip device as part of this study is identical to treatment with the MitraClip device outside of this study. Participation in the study will not impact the MitraClip procedure or use of the MitraClip in any way. Participation in the study requires submission of data that may or may not be protected health information. This information should be kept confidential, but there is a risk that some of the information could be unintentionally made non-confidential. The risk of this happening for this study is no greater than the risk of loss of confidentiality in any study.

14.5 Possible Interactions with Protocol-Required Concomitant Medications

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

14.6 Steps that will be Taken to Control or Mitigate the Risks

Per the device IFU, the following contraindications, warnings and precautions will be provided with all devices to be used during this study.

CONTRAINDICATIONS

Patients with the following conditions should not be treated with the MitraClip System:

Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen

Active endocarditis of the mitral valve

Rheumatic mitral valve disease

Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

WARNINGS

The following anatomic considerations may result in suboptimal leaflet insertion and/or MitraClip implantation. Patients with these conditions who undergo the MitraClip procedure may have an increased risk of serious adverse events which may be minimized with proper device usage and echocardiographic assessment. These events include the potential for increased procedure time, tissue injury, and/or worsening MR which may require additional MitraClip intervention or surgical treatment.

- Severe leaflet calcification in the grasping area
- Severe calcification of the annulus and/or subvalvular apparatus, such as the chordae tendinae
- Severely restricted posterior leaflet
- Cleft or perforation in the grasping area
- Leaflet Flail gap ≥ 10 mm and/or Leaflet Flail width ≥ 15 mm
- Coaptation length < 2 mm
- Intracardiac mass

The following anatomic considerations may result in serious adverse events, including tissue injury, worsening MR or in the case of the mitral valve area, mitral stenosis. If these events were to occur they can require additional percutaneous or surgical intervention for treatment. The occurrence of these events can be minimized with appropriate preoperative evaluation of the valve anatomy and regurgitant jet.

- Mitral valve orifice area < 4 cm²
- Primary regurgitant jet outside of the A2-P2 area and/or presence of a clinically significant 2nd jet

Patients with the following considerations in whom the Steerable Guide Catheter is used may have an increased risk of having a serious adverse event which may be avoided with preoperative evaluation and proper device usage.

- Previous interatrial septal patch or prosthetic atrial septal defect (ASD) closure device which could result in significant difficulty in visualization or technical challenges during transseptal puncture and/or introducing the SGC into the left atrium.
- Known or suspected unstable angina or myocardial infarction within the last 12 weeks could increase the procedural morbidity and mortality, due to increased hemodynamic stress secondary to general anesthesia.
- Patients with active infection have an increased risk of developing an intraoperative and/or postoperative infection, such as sepsis or soft tissue abscess.
- Known or suspected left atrial myxoma could result in thromboembolism and tissue injury due to difficulty with device positioning.
- Recent cerebrovascular event (CVA) may increase the procedural morbidity associated with a transcatheter intervention, such as recurrent stroke.

The MitraClip Implant should be implanted with sterile techniques using fluoroscopy and echocardiography (e.g. transesophageal [TEE] and transthoracic [TTE]) in a facility with on-site cardiac surgery and immediate access to a cardiac operating room.

Read all instructions carefully. Failure to follow these instructions, warnings and precautions may lead to device damage, user injury, or patient injury. Use universal precautions for biohazards and sharps while handling the MitraClip System to avoid user injury.

Use of the MitraClip System should be restricted to those physicians trained to perform invasive endovascular and transseptal procedures and those trained in the proper use of the system.

For the Clip Delivery System and Steerable Guide Catheter only: this device is designed for single use only. Cleaning, re-sterilization and / or re-use may result in infections, malfunction of the device and other serious injury or death.

PRECAUTIONS

NOTE the “Use by” date specified on the package.

Inspect all product prior to use. Do not use if the package is open or damaged, or if product is damaged.

14.7 Risk to Benefit Rationale

Subjects participating in this study will be receiving the latest technology in MitraClip which has been shown to be safe and effective in over 4,500 patients in clinical trials and more than 50,000 patients in worldwide use to date. This is a post-market study being conducted on an approved device within the standard of care procedures. The risks associated with receiving a MitraClip implant within this study are identical to the risks of receiving a MitraClip implant outside of the study.

Subjects participating in the study have a small risk of loss of confidentiality as part of the data collection process. This risk is mitigated to as low as possible with the use of data collection systems, methods and procedures that are used commonly in clinical research. This includes the use of only validated electronic systems, the training of study personnel and the use of de-identified data for all data entry.

Based upon the established safety profile of the MitraClip device; the low risk of loss of confidentiality is adequately mitigated to justify use of the next generation MitraClip to treat patients for this study.

APPENDIX I - ABBREVIATIONS AND ACRONYMS

A2-P2	Second location on anterior and posterior leaflets
AE	Adverse Event
APS	Acute Procedural Success
ASD	Atrial Septal Defect
CI	Confidence Interval
CRF	Case Report Form
CV	Cardiovascular
CVA	Cardiovascular Accident
DD	Device Deficiency
DM	Device Malfunction
DVT	Deep venous thrombus
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
GRASP	The GRASP Registry
IFU	Instructions for Use
IVC	Inferior Vena Cava
MAE	Major Adverse Event
MitraClip XTR	MitraClip XTR System
MOPs	Manual of Operations
MR	Mitral Regurgitation
NYHA	New York Heart Association
PMCF	Post Market Clinical Follow-Up
SAE	Serious Adverse Event
SLDA	Single leaflet device attachment
TEE	Transcatheter Esophageal Echocardiogram
TIA	Transient Ischemic Attack
TRAMI	Transcatheter Mitral Valve Interventions Study
TTE	Transcatheter Thoracic Echocardiogram
UADE	Unanticipated Adverse Device Event
USADE	Unanticipated Serious Adverse Device Event

APPENDIX II - DEFINITIONS

ANTICIPATED ADVERSE EVENT

Derived from ISO14155, MEDDEV 2.7.3: an effect which by its nature, incidence, severity or outcome has been previously identified as “POTENTIAL COMPLICATIONS AND ADVERSE EVENTS”, as documented in the IFU or CIP (**Appendix IV**).

DEATH (All Cause)

All deaths regardless of cause. Death is further divided into 2 categories

1. CARDIOVASCULAR DEATH (VARC)

Per the Valve Academic Research Consortium (VARC)⁵ as any one of the following:

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

2. NON-CARDIOVASCULAR DEATH

Any death not covered by the VARC definitions of Cardiovascular Death, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

DEVICE EMBOLIZATION

Detachment of the deployed MitraClip from the leaflets as assessed by the study site.

DEVICE THROMBOSIS

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

ENDOCARDITIS

A diagnosis of endocarditis based on the following 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)

Endocarditis is based on the confirmation of either Pathological Criteria or Clinical Criteria.

Diagnosis for Clinical Criteria of Endocarditis must at least meet 1 of the following combinations:

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

Pathological Criteria

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

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

OR

Clinical Criteria

Major Criteria

Persistently positive blood cultures:

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

Persistent bacteremia:

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

Evidence of endocardial involvement

Positive echocardiogram

Oscillating vegetation

Abscesses

Valve perforation

New partial dehiscence of prosthetic valve

New valvular regurgitation

Minor Criteria

Predisposing heart condition:

Mitral Valve Prolapse, 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

HOSPITALIZATION (ALL-CAUSE)

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

HEART FAILURE HOSPITALIZATION

Defined as an event that meets the following criteria:

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

AND

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

AND

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

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

OTHER CARDIOVASCULAR HOSPITALIZATION

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

NON-CARDIOVASCULAR HOSPITALIZATION

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

MAJOR ADVERSE EVENT (MAE)

MAE is a CEC-adjudicated composite of all-cause death, stroke, myocardial infarction, and non elective CV surgery for device related adverse events

MAJOR BLEEDING

Major bleeding is defined as bleeding \geq Type 3 based on a modified Bleeding Academic Research Consortium (BARC)³⁵ 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

³⁵ 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.

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥ 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

MAJOR VASCULAR COMPLICATION

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

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

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

OR

Mandatory: CK-MB ≥ 5 x 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 ≥ 10 x ULN (preferred) within 24 hrs. of cardiothoracic surgery *plus 1 of the following*:

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

Spontaneous MI (>72 hours after MitraClip procedure)

Any one of the following criteria:

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

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA CLASS)

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

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

Cardiovascular surgical procedure performed for device related complication requiring surgery within 24 hours of onset of adverse event, including events found during scheduled follow-up. 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 that may lead to non-elective cardiovascular surgery include, myocardial perforation, Single Leaflet Device Attachment (confirmed by Echo Core Lab), embolization of the MitraClip or MitraClip System components, iatrogenic atrial septal defect, or the need for valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip.

SINGLE LEAFLET DEVICE ATTACHMENT (SLDA)

Defined as unilateral MitraClip detachment from one leaflet as assessed by the study site and confirmed by the ECL. 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/CEREBROVASCULAR ACCIDENT and TIA

Cerebrovascular Accident (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 or 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, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist*

Confirmation of the diagnosis by at least one of the following:

- Neurologist or neurosurgical specialist
- Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification

Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined – An acute episode where there is insufficient information to allow categorization as ischemic or hemorrhagic.

Stroke definitions†

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

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

*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.

Tricuspid Regurgitation Severity

TR grading will be based on the 2017 ASE Guidelines (Zoghbi 2017)³⁶: Rating will be: none, mild, moderate, or severe.

Unanticipated Adverse Device Effect [UADE]

UADEs or 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 protocol 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. All reported adverse events are reviewed by Sponsor so that UADEs/USADEs are identified and addressed.

VULNERABLE POPULATION (ISO14155 Definition)

Defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects may include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

³⁶ Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017 Apr;30(4):303-371.

APPENDIX III - Case Report Forms

Data will be collected on electronic case report forms (eCRFs). The eCRFs will be made available before the study starts enrollment.

END OF MitraClip XTR PMCF Protocol

APPENDIX II: ABBREVIATIONS AND ACRONYM

A2-P2	Second location on anterior and posterior leaflets
ACCESS	ACCESS-EU Study
AE	Adverse Event
APS	Acute Procedural Success
ASD	Atrial Septal Defect
CDS	Clip Delivery System
CE	Conformité Européene
CEC	Clinical Events Committee
Co-PIs	Co-Primary Investigators
CRF	Case Report Form
CV	Cardiovascular
CVA	Cardiovascular Accident
DC	Delivery Catheter
DD	Device Deficiency
DM	Device Malfunction
DMR	Degenerative Mitral Regurgitation
DVT	Deep venous thrombus
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EROA	Effective Regurgitant Orifice Area
EU	European Union
Euroscore	European System for Cardiac Operative Risk Evaluation
EVEREST II	The EVEREST II Study
EXPAND	The MitraClip EXPAND Study
FDA	U.S. Food and Drug Administration
FMR	Functional Mitral Regurgitation
GCP	Good Clinical Practice
GRASP	The GRASP Registry
HIPAA	Health Insurance Portability and Accountability Act
HRR	High Risk Registry (part of EVEREST II)
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
IVC	Inferior Vena Cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVOT	Left Ventricle Outflow Tract

MAE	Major Adverse Event
MitraClip NT	MitraClip NT System
MitraClip NTR	MitraClip NTR System (new delivery system)
MitraClip XTR	MitraClip XTR System (new delivery system and longer clip arms)
MOPs	Manual of Operations
MR	Mitral Regurgitation
NYHA	New York Heart Association
PMCF	Post Market Clinical Follow-Up
QOL	Quality of Life
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAX	Short Axis
SGC	Steerable Guide Catheter
SLDA	Single leaflet device attachment
TEE	Transcatheter Esophageal Echocardiogram
TIA	Transient Ischemic Attack
TR	Tricuspid Regurgitation
TRAMI	Transcatheter Mitral Valve Interventions Study
TTE	Transcatheter Thoracic Echocardiogram
TVT	Transcatheter Valve Treatment Registry
UADE	Unanticipated Adverse Device Event
USADE	Unanticipated Serious Adverse Device Event

APPENDIX III: DEFINITIONS

DEATH (All Cause)

All deaths regardless of cause. Death is further divided into 2 categories

1. CARDIOVASCULAR DEATH (VARC)

Per the Valve Academic Research Consortium (VARC)⁵ as any one of the following:

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

3. NON-CARDIOVASCULAR DEATH

Any death not covered by the VARC definitions of Cardiovascular Death, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

DEVICE EMBOLIZATION

Detachment of the deployed MitraClip from the leaflets as assessed by the study site.

DEVICE THROMBOSIS

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

ENDOCARDITIS

A diagnosis of endocarditis based on the following 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)

Endocarditis is based on the confirmation of either Pathological Criteria or Clinical Criteria.

Diagnosis for Clinical Criteria of Endocarditis must at least meet 1 of the following combinations:

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

Pathological Criteria

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

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

OR

Clinical Criteria**Major Criteria**Persistently positive blood cultures:

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

Persistent bacteremia:

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

Evidence of endocardial involvement

Positive echocardiogram
Oscillating vegetation
Abscesses
Valve perforation
New partial dehiscence of prosthetic valve
New valvular regurgitation

Minor CriteriaPredisposing heart condition:

Mitral Valve Prolapse, bicuspid aortic valve, rheumatic or congenital heart disease, intravenous drug use

FeverVascular 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 criteriaEchocardiogram: positive but not meeting major criteria**HOSPITALIZATION (ALL-CAUSE)**

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

HEART FAILURE HOSPITALIZATION

Defined as an event that meets the following criteria:

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

AND

E. 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

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

OTHER CARDIOVASCULAR HOSPITALIZATION

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

NON-CARDIOVASCULAR HOSPITALIZATION

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

MAJOR ADVERSE EVENT (MAE)

MAE defined as a composite of all-cause Death, MI, Stroke, or non-elective CV surgery for device related complications (CEC adjudicated)

MAJOR BLEEDING

Major bleeding is defined as bleeding \geq Type 3 based on a modified Bleeding Academic Research Consortium (BARC)³⁷ definition:

- Type 3
 - Type 3a
 - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
 - Any transfusion with overt bleeding
 - Type 3b
 - Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed)
 - Cardiac tamponade
 - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
 - Bleeding requiring intravenous vasoactive agents
 - Type 3c
 - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
 - Subcategories confirmed by autopsy or imaging or lumbar puncture
 - Intraocular bleed compromising vision
- Type 4: CV Surgery-related bleeding
 - Perioperative intracranial bleeding within 48 h
 - Reoperation after closure of sternotomy for the purpose of controlling bleeding
 - Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period†
 - Chest tube output ≥ 2 L within a 24-h period
- Type 5: Fatal bleeding
 - Type 5a

³⁷ 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.

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

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin)

†Cell saver products are not counted

MAJOR VASCULAR COMPLICATION

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

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

MYOCARDIAL INFARCTION

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

Peri-procedural MI (≤ 72 hours after MitraClip procedure)

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

OR

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

Post-surgery

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

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

Spontaneous MI (>72 hours after MitraClip procedure)

Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (CK-MB) with at least one value above the upper limits of normal (ULN), together with evidence of myocardial ischemia with at least one of the following:
 - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
 - New pathological Q waves in at least two contiguous leads

- Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA CLASS)

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

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

Cardiovascular surgical procedure performed for device related complication requiring surgery within 24 hours of onset of adverse event, including events found during scheduled follow-up. 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 that may lead to non-elective cardiovascular surgery include, myocardial perforation, Single Leaflet Device Attachment (confirmed by Echo Core Lab), embolization of the MitraClip or MitraClip System components, iatrogenic atrial septal defect, or the need for valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip.

SINGLE LEAFLET DEVICE ATTACHMENT (SLDA)

Defined as unilateral MitraClip detachment from one leaflet as assessed by the study site and confirmed by the ECL. 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/CEREBROVASCULAR ACCIDENT and TIA

Cerebrovascular Accident (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 or 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, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist*

Confirmation of the diagnosis by at least one of the following:

- Neurologist or neurosurgical specialist
- Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification

Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined – An acute episode where there is insufficient information to allow categorization as ischemic or hemorrhagic.

Stroke definitions†

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

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

*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 Adverse Device Effect [UADE]

UADEs or 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 protocol 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. All reported adverse events are reviewed by Sponsor so that UADEs/USADEs are identified and addressed.

VULNERABLE POPULATION (ISO14155 Definition)

Defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects may include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

APPENDIX IV: LITERATURE REVIEW AND SUMMARY OF PRECLINICAL TRIALS**CINICAL TRIALS**

In the United States, the MitraClip System has been studied under an Investigational Device Exemption (IDE G030064). The IDE consists of the following cohorts:

- 1) Phase I Feasibility Study (EVEREST I)
- 1) Phase II Safety / Effectiveness Study (EVEREST II)
 - a) EVEREST II Roll-In
 - b) EVEREST II Randomized Controlled Trial Arm
 - c) EVEREST II High Risk Registry Arm
- 2) Phase II Continued Access Study (REALISM)
 - a) Non-High Risk Arm
 - b) High Risk Arm
 - c) Emergency Use/Compassionate Use cases

1) *EVEREST I*

EVEREST I³⁸ was initiated on July 2, 2003 and enrollment concluded on February 15, 2006. A total of 55 patients were enrolled and treated in EVEREST I. The EVEREST I Feasibility trial was the first prospective, multi-center, non-randomized trial to evaluate the preliminary safety and effectiveness of the percutaneous MitraClip System in patients with moderate-to-severe (3+) or severe (4+) MR in surgical candidates. Percutaneously-treated patients were followed at discharge, 30 days, 6, 12, 18 and 24 months and annually thereafter through 5 years. An independent Echocardiography Core Laboratory (ECL) assessed MR severity and other echocardiographic parameters at baseline and follow-up. The last patient has completed 5-year follow-up and the study is now closed.

The MitraClip device was implanted in 89% (49/55) of patients and the trial met its pre-specified safety acceptance criterion, demonstrating mechanistic feasibility of implant and safety of the MitraClip System and procedure. There were no intra-procedural deaths. Acute procedural success was achieved in 70.9% of patients. A majority of patients (83.3%) implanted with a MitraClip device experienced reduction in MR severity to 2+ or less at discharge. No MitraClip device embolizations occurred in this cohort. Ten percent (10%) of the initial cohort had single leaflet device attachment (SLDA). A majority of SLDAs were detected early (within 30 days post-MitraClip procedure). Patients demonstrated improvement in NYHA Functional Class and left ventricular measurements that were sustained through 5 years. At 5 years, freedom from death was 86.4% and freedom from mitral valve surgery was 55.1%. The results of the EVEREST I trial at 5 years provide evidence of the safety and long-term durability of the MitraClip device in the early cohort of patients treated in the United States.

³⁸ IDE G030064/ P100009/A017 EVEREST I Final Clinical Report Version 1.0 - 17/Nov/2011

2) **EVEREST II**

a. **Randomized Clinical Trial (RCT)**³⁹

The EVEREST II RCT^{40, 41, 42} is a prospective, multi-center, randomized controlled trial where patients with moderate-to-severe (3+) or severe (4+) MR were randomized in a 2:1 ratio between the Device group (MitraClip device) and the Control group (mitral valve surgery). Patient follow-up occurs at discharge, 30 days, 6, 12, 18 and 24 months and yearly thereafter through 5 years. An independent Echocardiography Core Laboratory (ECL) assessed MR severity and other echocardiographic parameters at baseline and follow-up. The trial was intended to demonstrate superiority of safety balanced against reduced effectiveness of the MitraClip device when compared to mitral valve surgery. All patients have completed 5 years of follow-up and the study is now closed.

The trial enrolled 279 patients: 184 were randomized in the Device group and 95 were randomized in the Control group. Of these, 178 patients in the Device group underwent the MitraClip procedure and 80 patients in the Control group underwent mitral valve surgery. The trial met both primary safety and effectiveness endpoints. There were no intra-procedural deaths. Among patients who underwent the MitraClip procedure in the Device group (MitraClip patients), a device was implanted in 89% of patients. The procedure time averaged approximately 3 hours, patients were hemodynamically stable during the procedure, and the average length of hospital stay was 2.6 days. In comparison, the average length of hospital stay for patients undergoing surgery in the Control group (surgery patients) was 7.5 days. A large majority (94.9%) of MitraClip patients were discharged home without home healthcare. In comparison, only 71.3% of surgery patients were discharged home without home healthcare. Acute procedural success (APS) was achieved in 77% of patient treated in the Device Group. A majority of patients implanted with the MitraClip device (784) experienced reduction in MR severity to 2+ or less at discharge, while 100% of patients undergoing mitral valve surgery in the Control group experienced reduction in MR severity to 2+ or less.

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

³⁹ EVEREST II Randomized Controlled Trial (RCT) -0401– Five Year Final Report, Report Version 1.0 - 03/Nov/2014

⁴⁰ Mauri L, Garg P, Massaro JM, Foster E, Glower D, Mehoudar P, Powell F, Komtebedde J, McDermott E, Feldman T. The EVEREST II Trial: Design and Rationale for a Randomized Study of the Evalve MitraClip System Compared with Mitral Valve Surgery for Mitral Regurgitation. *Am Heart J.* 2010; 160:23-29.

⁴¹ Feldman T, Foster E, Glower DD, 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, Mauri L, Investigators EI. Percutaneous Repair or Surgery for Mitral Regurgitation. *N Engl J Med.* 2011; 364:1395-1406.

⁴² Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, Apruzzese P, Fail P, Rinaldi MJ, Smalling RW, Hermiller JB, Heimansohn D, Gray WA, Grayburn PA, Mack MJ, Lim DS, Ailawadi G, Herrmann HC, Acker MA, Silvestry FE, Foster E, Wang A, Glower DD, Mauri L, Investigators EI. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol.* 2015; 66:2844-2854.

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

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

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

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

Overall, the MitraClip clinical trials have shown consistently excellent safety and efficacy profile. Reduction of MR severity has shown improvements in symptoms, improved quality of life measurements, and functional improvements in patients who had significant MR.

b. EVEREST II High Risk Registry (HRR)⁴³

The EVEREST II High Risk Registry⁴⁴ is a single-arm prospective, multi-center, clinical trial designed to evaluate the safety and effectiveness of the MitraClip System in patients with moderate-to-severe (3+) or severe (4+) MR considered to be at high risk of surgical mortality. High risk was defined as predicted procedural mortality risk calculated using the STS surgical risk calculator of $\geq 12\%$ or in the judgment of the surgeon investigator the patient was considered a high risk surgical candidate due to the presence of specific protocol-defined criteria.

The primary objective of the EVEREST II HRR was to assess procedural safety in high surgical risk patients. Accordingly, the primary safety endpoint was procedural mortality at 30 days or prior to discharge compared to predicted surgical mortality. Secondary effectiveness measures were similar to those in the EVEREST II RCT, including changes in ECL-assessed measures of left ventricular function, NYHA functional class and SF-36 quality of life score at 1 year compared to baseline. Rate of hospitalizations for heart failure 1-year pre- and 1-year post-MitraClip was added as a descriptive endpoint for the EVEREST II HRR.

The EVEREST II HRR study enrolled 78 patients at 25 centers. Implant success in the EVEREST II HRR was high with 96.2% of patients implanted with one (59.0%) or two (37.2%) MitraClip devices. The mean post-procedure ICU/CCU/PACU stay was 2.2 days and the mean hospital stay was 3.9 days with

⁴³ EVEREST II High Risk Registry (HRR) – 0401 - Five Year Final Report, Report Version 1.0 – 03/Nov/2014

⁴⁴ Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, Bajwa T, Herrmann HC, Lasala J, Maddux JT, Tuzcu M, Kapadia S, Trento A, Siegel RJ, Foster E, Glower D, Mauri L, Kar S, Investigators EI. Acute and 12-Month Results with Catheter-Based Mitral Valve Leaflet Repair: The EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol.* 2012; 59:130-139.

a median of 2 days. Approximately 75% of patients were discharged home without the need for professional home healthcare. An additional 10% were discharged home with home healthcare required, resulting in a total of almost 86% being discharged home after the MitraClip procedure. At discharge, MR was reduced in a majority of patients (74.7%) to $\leq 2+$ and in 40% of patients to $\leq 1+$.

The primary safety endpoint of procedural mortality (observed vs. predicted) was met. The observed procedural mortality rate at 30 days was 7.7% (95.472% UCB=14.8%) and compared favorably ($p=0.006$) to the average predicted surgical mortality of 18.2%. The observed procedural mortality rate was also lower when compared to the average STS mortality risk (14.2%).

Among patients with paired data at baseline and 1 year, MR reduction was sustained to $\leq 2+$ in 77.8% of patients and to $\leq 1+$ in 31.5% of patients. Significant improvement in NYHA Class was observed at 1 year in the EVEREST II HRR. Among patients with paired data at baseline and 1 year, the proportion of patients with NYHA Class III or IV reduced from 88.9% at baseline to 25.9% at 1 year. Improvement in both physical and mental components of the SF-36 quality of life by 4.0 and 3.2 points respectively were observed at 1 year. A significant decrease in the rate of heart failure hospitalizations (0.65 to 0.36 per patient-year) was observed in the year following the MitraClip procedure compared to the year prior.

Adverse events occurred at rates as expected in the advanced age patient population with significant comorbidities. The MAE rate at 30 days was 26.9%, with transfusions ≥ 2 units comprising the majority of events (17.9%). There was no incidence of non-elective (urgent/emergent) cardiovascular surgery for adverse events or new onset of persistent atrial fibrillation in this cohort through 1 year.

After the initial 30 days post-procedure, site-reported adverse events (AE) occurred at a steady low rate as expected for this population. The most commonly site-reported AEs through 5 years were cardiac, renal and vascular. The most commonly reported cardiac AE were congestive heart failure, atrial arrhythmia, peripheral edema and syncope. The most commonly reported renal AE were renal insufficiency/failure and infection. The most commonly reported vascular AE was hemodynamic instability. These rates are as expected for a percutaneous procedure in elderly patients with multiple baseline co-morbidities.

Device complications were rare; the rate of single leaflet device attachment (SLDA) was 1.3% in the first year with no new occurrences reported thereafter. Only 2 patients had confirmed mitral stenosis through 5 years.

Through 5 years, a total of 42 (53.8%) deaths occurred in the EVEREST II HRR. This mortality rate is as expected due to the high risk nature of the patient population. At 5 years, MR reduction was sustained to $\leq 2+$ in 73.9% of surviving patients with paired data and to $\leq 1+$ in 47.8% of surviving patients with paired data. Among patients with paired data at baseline and 5 years, the proportion of surviving patients with NYHA Class III or IV reduced from 89.7% at baseline to 18.9%, 9.7%, and 16.7% at 3 years, 4 years and 5 years, respectively. LVEDV and LVESV are significantly reduced at 5 years following the MitraClip procedure. These reductions are indicative of left ventricular reverse remodeling associated with MR reduction.

These data from the EVEREST II HRR suggest a role for the MitraClip device in treating symptomatic patients with 3+ to 4+ MR who are at high risk of mortality with MV surgery. MitraClip device placement in this selected high-risk group is feasible, effective in reducing symptoms and improving clinical status, and relatively safe in patients who otherwise have no safe option to reduce MR.

3) REALISM Continued Access

The EVEREST II REALISM study is a continued access registry designed for continued data collection on the use of the MitraClip System in “real world” conditions. After the completion of enrollment in the pivotal EVEREST II RCT and EVEREST II HRR study, continued access to the technology was warranted to collect additional safety and effectiveness data on the MitraClip device. There are two arms (High Risk and Non-High Risk) in the REALISM study. Enrollment in the Non-High Risk arm of the study concluded on April 14, 2011, and enrollment in the High Risk arm concluded on December 19, 2013. Patients with serious or life-threatening conditions that did not meet REALISM High Risk or Non-High Risk eligibility criteria were evaluated for consideration for either Emergency Use (EU) or Compassionate Use (CU).

Each arm of the REALISM study was designed with inclusion/exclusion criteria and endpoints aligned to maintain consistency with the EVEREST II RCT and HRR studies. Eligibility criteria in REALISM HR are identical to EVEREST II HRR, with one exception: patients are excluded from REALISM HR if they had a concurrent medical condition resulting in a life expectancy of less than 1 year. This criterion was added to exclude terminally ill patients, including those in hospice. Safety, effectiveness and follow-up data collection in REALISM HR are identical to EVEREST II HRR, with enrollment and follow-up ongoing through 5 years.

a. REALISM Non-High Risk Arm⁴⁵

A total of 271 patients have been enrolled in the non-high risk arm of REALISM. MitraClip implant rate was 95.2%. Post-procedure, the average duration of hospitalization was 2.8 days. The mean duration of stay in the ICU/CCU/PACU post-procedure was 28.8 hours, and a majority of patients (91.5%) returned home post procedure and required no home-health care. Two patients (0.7%) died prior to discharge of non-cardiac causes.

At the 30-day and 12-month time points, 11.4% and 27.3% of the participants respectively experienced MAEs as adjudicated by the CEC. A total of 27 deaths were reported during the 12-month follow-up window (410 days). Thirteen of the 27 deaths were CEC-adjudicated to cardiac causes. Interim Kaplan-Meier analysis at 5 years demonstrated an event-free survival rate of 61.0%. The incidence of SLDA after index procedure was reported in 11 (4.3%) of the 258 patients who received at least one MitraClip device in the Non-High Risk arm. No cases of MitraClip procedure-related embolizations were reported.

Reduction to MR $\leq 2+$ was achieved in 89% of patients at 30 days and in 84% of patients at 12 months. A similar trend was observed at subsequent follow-ups with a majority (>75%) of patients with MR severity remaining consistently mild to moderate. A reduction was observed in LV dimensions and volumes measured with echocardiography on analysis of matched data up to 60 months, which was consistent with the reduction in MR severity and indicative of LV remodeling.

An overall improvement in cardiac status was observed, with more than 88.0% of the treated patients being categorized as NYHA Class I or II through follow-up visits which indicated an improvement in the symptomatic status and was consistent with the results of MR severity improvement and LV remodeling. Statistically significant improvements in SF-36 PCS quality of life scores and clinically meaningful improvements in SF-36 quality of life MCS scores were observed at 30 days and 12 months.

The results of the non-high risk arm of the REALISM study are consistent with the findings from the previously conducted studies for the MitraClip Device including the pivotal EVEREST II RCT.

⁴⁵ EVEREST II REALISM– Non-High Risk 2017 Annual Report, Protocol #0401- Clinical Investigation Report Ver 1.0 - 24/APR/2017

b. REALISM High Risk Arm⁴⁶

A total of 628 patients have been enrolled in the high risk arm of REALISM. A majority of patients had multiple pre-existing co-morbidities at baseline and were considered high risk for mitral valve surgery. The mean STS mortality risk score of this high-risk population was 11.1%, with 43.5% of patients having a mortality risk score $\geq 12\%$.

In the high-risk cohort, the MitraClip implant rate was 96%, with 53% of the patients receiving a single MitraClip device and 43% of the patients receiving multiple devices. Following the intervention, patients spent a mean duration of 36.5 hours in the ICU/CCU/PACU during an average hospital stay of 3.2 days. A majority (83.3%) of the patients returned home with no further need for assisted healthcare. Twelve patients (1.9%) died before discharge.

The CEC-adjudicated major adverse event (MAE) rates including transfusions were 15.6% at 30 days and 35.4% at 12 months. A total of 146 deaths were reported up to the 12-month follow-up window (410 days). Of these 146 deaths, 97 (66.4%) were adjudicated as cardiac-related and 49 (33.6%) were adjudicated as non-cardiac related. There were no reports of MitraClip device embolization during the study. Of the 603 patients who had at least one MitraClip device implanted, 13 cases of single leaflet Device attachment (SLDA) were noted.

Reduction to MR $\leq 2+$ was achieved in 90% of patients at discharge/30 days and in 85% of patients at 12 months. A similar trend was observed at subsequent follow-ups with a majority ($>80\%$) of patients with MR severity remaining consistently mild to moderate. A steady reduction in LV volume and dimensions was observed through 60 months, which indicated that a reverse LV remodeling occurred following implantation of the MitraClip device. There was a significant improvement from baseline of 35.2 meters in mean distance walked in 6-minute walk test (6MWT) at 12 months. There were statistically significant improvements in the physical component score (PCS) and mental component score (MCS) domains of the SF-36 QoL scores at both 30 days and 12 months.

There was a reduction in the proportion of patients hospitalized and events leading to hospitalization for CHF from the pre-enrollment time-point (36.6% and 402, respectively) to the 12-month follow-up (17.8% and 174, respectively).

Safety and Device efficacy data from the high-risk arm of the REALISM study show that the MitraClip is a viable option for treatment of degenerative and functional MR in high-risk individuals who carry a 30-day STS-calculated or surgeon-assessed mortality risk $\geq 12\%$. Follow-up through 5 years demonstrates that the MitraClip procedure and device have an acceptable safety profile and that outcomes are durable. Long-term survival of this high-risk cohort is as expected considering their baseline incidence of multiple major co-morbidities.

Commercial Experience

The MitraClip System received approval for commercialization in Europe in March 2008, and is indicated for reconstruction of the insufficient mitral valve through tissue approximation. This broad indication has allowed early commercial use to depart from patients traditionally treated in the EVEREST II RCT clinical trial, which was limited to surgical candidates, mainly with preserved LV function and degenerative valve

⁴⁶ EVEREST II REALISM– High Risk 2017 Annual Report, Protocol #0401- Clinical Investigation Report Ver 1.0 24/Apr/2017

disease, and move towards increasingly higher surgical risk patients featuring more complex mitral valve anatomies.

One such early example of the expanded use of the MitraClip therapy in contemporary clinical practice was published by Franzen et al.⁴⁷ who sought to evaluate the outcomes of the MitraClip device in a cohort of high surgical risk patients without applying any of the rigid EVEREST II exclusion criteria. Of 51 consecutive patients treated with the MitraClip device at the Hamburg University Heart Centre between September 2008 and July 2009, 35 (69%) had LV characteristics and/or a mitral valve morphology that would have excluded them from enrolment in the EVEREST I and II trials. The positive acute outcomes achieved in these patients paved the way for larger contemporary commercial registries, the most prominent of which are summarized below:

ACCESS-EU Phase I

ACCESS-EU⁴⁸ was a two-phase prospective, single-arm, multicenter post-approval observational study of the MitraClip in Europe for the treatment of MR sponsored by Abbott Vascular. The primary objective of the ACCESS-EU study was to gain information with respect to health economics and clinical care, and to provide further evidence of safety and effectiveness. Five hundred sixty-seven (567) patients were treated with the MitraClip in Europe. One-year clinical follow-up was available in 487 patients. The study is now closed.

Patients in ACCESS-EU had a mean age of 73.7 years and were predominantly males (63.8%). A majority (77.1%) had functional MR. At baseline, 84.9% were in NYHA functional class III or IV, and the mean LVEF was 35%. The mean logistic EuroScore was 23.0% with approximately half of patients having a logistic EuroScore of 20% or greater. Despite the broad indication for the MitraClip in Europe, the patients treated in the ACCESS-EU study were representative of the higher end of the surgical risk spectrum.

Patients enrolled in ACCESS-EU represent a population with significant, symptomatic MR, a high rate of multiple serious comorbidities. Considering the high MitraClip device implant rate (99.6%, 565/567), the high rate of meaningful MR reduction (78.9%, 258/327 MR<2+), and the resulting improvements in 6-minute walk (59.5 m difference, $p<0.0001$), Minnesota Living with Heart Failure Questionnaire quality of life score (13.5 point improvement, $p<0.0001$) and NYHA Functional Class (71.5% NYHA Class I or II, $p<0.0001$), at 1 year, it is concluded that the MitraClip device provides an important therapeutic option for patients with significant mitral regurgitation, and is an especially important option for patients who may be considered high surgical risk.

Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP)

The GRASP registry is a single-center, prospective, observational study of consecutive high surgical risk patients with moderate-to-severe or severe MR undergoing percutaneous mitral valve repair with the MitraClip System at Ferrarotto Hospital (Catania, Italy). The study does not have specific exclusion criteria; and the indication for MitraClip therapy is established by a multidisciplinary Heart Team. The

⁴⁷ Franzen O, Baldus S, Rudolph V, Meyer S, Knap M, Koschyk D, Treede H, Barmeyer A, Schofer J, Costard-Jackle A, Schluter M, Reichenspurner H, Meinertz T. Acute Outcomes of MitraClip Therapy for Mitral Regurgitation in High-Surgical-Risk Patients: Emphasis on Adverse Valve Morphology and Severe Left Ventricular Dysfunction. *Eur Heart J*. 2010; 31:1373-1381.

⁴⁸ Maisano F, Franzen O, Baldus S, Schafer 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 1-Year Results from the ACCESS-EU, a Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe. *J Am Coll Cardiol*. 2013; 62:1052-1061.

degree of preprocedural MR is quantified according to current guidelines by two expert echocardiographers.

A total of 117 consecutive patients underwent MitraClip implantation between August 2008 and October 2012 as part of the ongoing GRASP registry⁴⁹. Mean age was 72±10 years and 67% were male. The mean logistic EuroSCORE was 12±14%, and a majority (76%) of patients had functional MR. MR grade 3+ or 4+ was present in 98% of patients, and NYHA functional class symptoms in 80% of patients. At baseline, 63% of patients met the EVEREST leaflet anatomic criteria (i.e., coaptation depth <11 mm, coaptation length >2 mm).

Acute procedural success was achieved in all patients. MR was reduced to 1+ and 2+ post-procedure in 63% and 37% of patients, respectively.

The primary safety end point was the rate of major adverse events (MAEs) at 30 days, defined as the composite of death, myocardial infarction, reoperation for failed mitral valve surgery, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for >48 hours, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of ≥2 units of blood. The primary efficacy end point was freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR at 30 days and 1 year after clip implantation.

MAEs occurred in 4 patients (4.3%) at 30 days. One patient died from gastrointestinal bleeding within 30 days. Ten additional patients died within 1 year for a total of 11 deaths. Another 8 patients died between 1- and 3-years post-procedure.

Deterioration to MR ≥3+ was recorded in 25% of patients with degenerative MR and 7% of those with functional MR at 1 year. No surgery for mitral valve dysfunction was needed within the first year after clip implantation. No cases of clip detachment or embolization were observed. Kaplan-Meier estimates of freedom from the primary efficacy endpoint was 96.4% at 30 days and 75.8% at 1 year. No survival difference was noted based on MR etiology.

Results from the GRASP registry support the safety and efficacy of the MitraClip device in a real-world setting.

GRASP Registry: EVEREST_{ON} versus EVEREST_{OFF} Criteria

Attizzani et al.⁵⁰ analyzed the outcomes of GRASP patients according to baseline echocardiographic criteria. Patients who did not meet the EVEREST echocardiographic criteria were assigned to the investigational group (EVEREST_{OFF}; N=93), whereas those meeting the EVEREST echocardiographic

⁴⁹ Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistrutto A, Ministeri M, Barbanti M, Caggegi A, Chiaranda M, Dipasqua F, Giaquinta S, Occhipinti M, Ussia G, Tamburino C. One- and Twelve-Month Safety and Efficacy Outcomes of Patients Undergoing Edge-to-Edge Percutaneous Mitral Valve Repair (from the GRASP Registry). *Am J Cardiol.* 2013; 111:1482-1487.

⁵⁰ Attizzani GF, Ohno Y, Capodanno D, Cannata S, Dipasqua F, Imme S, Mangiafico S, Barbanti M, Ministeri M, Caggegi A, Pistrutto AM, Giaquinta S, Farruggio S, Chiaranda M, Ronsivalle G, Schnell A, Scandura S, Tamburino C, Capranzano P, Grasso C. Extended Use of Percutaneous Edge-to-Edge Mitral Valve Repair Beyond EVEREST (Endovascular Valve Edge-to-Edge Repair) Criteria: 30-Day and 12-Month Clinical and Echocardiographic Outcomes from the GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) Registry. *JACC Cardiovasc Interv.* 2015; 8:74-82.

criteria were assigned to the control group (EVEREST_{ON}; N=78). Among the 93 patients included in the EVEREST_{OFF} group, 35 patients had LVEF \leq 25%, 28 patients had LV end systolic diameter $>$ 55 mm, 34 patients had coaptation depth \geq 11 mm, and 10 patients had the flail width \geq 15 mm. Otherwise, baseline characteristics were comparable between the two groups.

High rates of acute procedural success were achieved in both groups (97.8% and 100% for EVEREST_{OFF} and EVEREST_{ON}, respectively). At 30-days, the rate of MAEs (i.e. primary safety endpoint) was comparable between groups (2.6% vs. 6.5%, respectively, $p=0.204$). Freedom from death, surgery for mitral valve dysfunction, or grade \geq 3+ MR (i.e. primary effectiveness endpoint) was 90.1% and 93.5%, respectively ($p=0.427$). Reduction in MR severity, symptomatic improvements, and re-hospitalizations for heart failure were comparable between the two groups.

At 1 year, Kaplan-Meier freedom from the primary efficacy endpoint was demonstrated in 71.4% and 76.2%, respectively, in the EVEREST_{OFF} and EVEREST_{ON} groups. Approximately 90% of surviving patients in both groups had sustained MR reduction to \leq 2+, and approximately 78% of patients from both groups had NYHA functional class I or II at 1 year.

A sub-group analysis of the EVEREST_{OFF} patients evaluated the impact of different characteristics of enrollment based on 1) valve geometry, 2) ventricle function/geometry, and 3) a combination of the two. Although the combined group revealed numerically lower efficacy (primary efficacy endpoint 76.2%, 75%, and 62.5%, respectively, $p=0.521$), higher rates of MR \geq 3+ (14.5%, 12.5%, and 20.8%, $p=0.710$), as well as higher death rates (9.5%, 12.5%, and 25%, respectively, $p=0.312$), these differences did not reach statistical significance.

This analysis of the GRASP Registry suggests that MitraClip implantation in patients with expanded baseline echocardiographic features was associated with similar rates of safety and efficacy through 12-month follow-up when compared with patients meeting the EVEREST anatomical criteria.

The German Transcatheter Mitral Valve Interventions (TRAMI)

The German transcatheter mitral valve interventions (TRAMI) registry was initiated in August 2010 to collect data from clinical centers in Germany involved in transcatheter therapies for mitral valve disease. The registry comprises a retrospective part, including patients who have been treated at individual sites prior to study initiation, and a prospective part after study site initiation. Follow-up for the retrospective part was not defined in the study protocol and was performed according to institutional practice. Follow-up for the prospective part was scheduled at 30 days and then at 1, 3, and 5 years. Enrollment in TRAMI is ongoing.

Several reports on TRAMI have been published over the years^{51,52}. The largest prospective cohort was described by Puls et al.⁵³. A total of 828 patients were prospectively enrolled at 21 German sites between 2010 and 2013. One-year follow-up was available in 749 patients.

⁵¹ Baldus S, Schillinger W, Franzen O, Bekeredjian R, Sievert H, Schofer J, Kuck KH, Konorza T, Mollmann H, Hehrlein C, Ouarrak T, Senges J, Meinertz T, investigators GTMVI. MitraClip Therapy in Daily Clinical Practice: Initial Results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. *Eur J Heart Fail.* 2012; 14:1050-1055.

⁵² Schillinger W, Hunlich M, Baldus S, Ouarrak T, Boekstegers P, Hink U, Butter C, Bekeredjian R, Plicht B, Sievert H, Schofer J, Senges J, Meinertz T, Hasenfuss G. Acute Outcomes after MitraClip Therapy in Highly Aged Patients: Results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. *EuroIntervention.* 2013; 9:84-90.

⁵³ Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-Year Outcomes and Predictors of Mortality after MitraClip Protocol 17-518: Version 2.0

Patients had an average age of 76 years and a majority (89%) were symptomatic with NYHA functional class III or IV. Median STS mortality risk score was 6.0%. Approximately 70% of patients underwent the MitraClip procedure for functional MR. The MitraClip implant rate in this cohort was 97%, with an average of 1.4 ± 0.6 clips implanted per procedure. Mean procedure time and fluoroscopy duration were 102.8 ± 54.1 minutes and 28.8 ± 57.9 minutes, respectively. Mitral regurgitation was reduced from severe (94%) at baseline to none or mild in 85.2% of patients post procedure.

One patient died intra-operatively and in-hospital mortality was 2.4% (n=18). No emergent cardiac surgery was required. The rate of in-hospital Major adverse cardiac and cerebrovascular events (MACCE) was 3.1%. Other in-hospital major complications occurred in 12.8% of patients and were mainly associated with major bleeding complications. Five (0.7%) cases of SLDA were reported in this cohort. The median length of hospital stay was 9 days, and a majority (89.3%) were discharged to their normal social environment.

Thirty-day and 1-year mortality were 4.5% and 20.3%, respectively. The rates of transient ischemic attack (TIA; 3.8%), stroke (2.1%), and myocardial infarction (0.9%) at 1-year were low. A total of 8.5% of patients underwent a subsequent mitral valve surgery (2.3%) or second MitraClip device intervention (5.2%), respectively, to correct recurring MR. A majority (63.3%) of patients were in NYHA functional class I or II at 1-year and significant improvement in quality of life was observed using the EuroQuol visual analogue scale (EQ-5D).

Predictors of 1-year mortality included NYHA class IV, anemia, previous aortic valve intervention, serum creatinine ≥ 1.5 mg/dL, peripheral artery disease, LVEF 30%, severe tricuspid regurgitation, and procedural failure (defined as operator-reported failure, conversion to surgery, failure of clip placement, or residual post-procedural severe mitral regurgitation).

These results demonstrate that treatment of significant MR with the MitraClip device is efficacious and results in significant clinical improvements in a high proportion of TRAMI patients after 12 months. In this cohort, failure to achieve procedural success had the highest hazard ratio for predicting 1-year mortality.

Transcatheter Valve Treatment Sentinel Pilot Registry

The Transcatheter Valve Treatment Sentinel Pilot Registry is part of the European Society of Cardiology EuroObservational Research Programme and reports acute and 12-month follow-up results of 628 consecutive patients treated between January 2011 and December 2012 in 25 centers in 8 European countries.

Mean age of the patients entered in the registry was 74.2 ± 9.7 years, 63.1% were male, and 72.0% had functional MR. A majority (85.5%) of patients were in NYHA functional class III or IV at baseline. Mean logistic EuroSCORE was $20.4 \pm 16.7\%$, indicative of population of patients at high risk for surgical mortality.

Acute procedural success was high (95.4%) with no difference between FMR and DMR patients. Overall, in-hospital mortality was 2.9%. MR reduction to $\leq 2+$ was achieved in 98.2% of patients post-procedure with no difference between MR etiologies. At 1-year, MR was reduced to $\leq 2+$ in 94.0% of patients and

Therapy in Contemporary Clinical Practice: Results from the German Transcatheter Mitral Valve Interventions Registry. *Eur Heart J.* 2016; 37:703-712.

58.6% had mild or no MR, with comparable results obtained for FMR and DMR. A majority (74.2%) of patients were in NYHA functional class I or II at 1-year.

At 1-year, mortality was 15.3%, without significant differences between groups (FMR 15.0% vs. DMR 16.2%, $p[\log\text{-rank}]=0.650$). The estimated 1-year rate of heart failure re-hospitalization was 22.8% and was significantly higher in the FMR group compared to the DMR group (25.8% vs. 12%, $p[\log\text{-rank}]=0.009$). Freedom from the composite endpoint of death or re-hospitalization for heart failure was 69.0%, with no difference between FMR and DMR ($p[\log\text{ rank}]=0.103$). Multivariate analysis showed that EuroSCORE and successful deployment of the MitraClip device were independently associated with the composite endpoint at 1 year.

Re-intervention for recurring MR was infrequent with 2.9% of patients requiring a second MitraClip intervention and 0.9% requiring mitral valve surgery.

The results of the pilot European Sentinel Registry demonstrated that procedural and late mortality was low and lower than expected in such a high-risk cohort, without differences between FMR and DMR. These results confirm long-term benefits previously reported in other real-world registries.

MitraClip Asia-Pacific Registry (MARS)

MitraClip in the Asia-Pacific Registry (MARS)⁵⁴ is a multicenter retrospective registry that includes patients treated at 8 centers in Australia, China, Indonesia, Malaysia and Singapore. The study did not mandate specific anatomic requirements beyond the technical feasibility of grasping the mitral leaflets and patients who did not present with central mitral regurgitation involving A2/P2 segments were deemed eligible for enrollment.

A total of 145 patients underwent the MitraClip procedure between February 2011 to October 2013. Patients were predominantly male (64%) with a mean age was 71.4 ± 11.9 years. At baseline, all patients had MR severity 3+ (19%) or 4+ (81%). Functional MR etiology was present in 53.5%. A majority (68.3%) of patients were symptomatic with NYHA functional class III or IV at baseline. Mean STS score for the cohort was $7.4\pm 8.1\%$.

The MitraClip implant rate was 97.9% and the average procedure time was 130 ± 98 minutes. Acute procedural success was achieved in 93.7% (133/142). One MitraClip device was implanted in 70 (49.3%) patients, whereas 72 (50.7%) patients received ≥ 2 devices. There were no device embolization and 6 (4.2%) patients experienced an SLDA. The mean length of hospital stay post-procedure was 6.0 ± 7.8 days.

The 30-day mortality rate was 5.6% ($n=8$), while the 30-day MAE rate, defined as a composite of stroke, myocardial infarction, bleeding requiring transfusions >1 unit of blood, septicemia, reoperation for failed mitral valve procedure, non-elective cardiac surgery for adverse events, renal failure, gastrointestinal complications requiring surgery, ventilation for >48 hours, and new onset of atrial fibrillation was 12.7% (18/142).

At 30 days, 76.8% of patients had MR $\leq 2+$, with no significant differences observed between the FMR and DMR sub-groups. There was significant improvement in NYHA functional class with 82.1% of patients in class I or II at 30 days compared to 31.7% at baseline. At 30 days, there was a significant

⁵⁴ Yeo KK, Yap J, Yamen E, Muda N, Tay E, Walters DL, Santoso T, Liu X, Jansz P, Yip J, Zambahari R, Passage J, Koh TH, Wang J, Scalia G, Kuntjoro I, Soesanto AM, Muller D. Percutaneous Mitral Valve Repair with the MitraClip: Early Results from the MitraClip Asia-Pacific Registry (MARS). *EuroIntervention*. 2014; 10:620-625.

reduction in LVEF, LVEDD, LVESD, LA indexed volume and calculated pulmonary artery systolic pressure compared to baseline.

In a separate analysis, Tay et al.⁵⁵ described and compared the use of the MitraClip therapy in patients with FMR and DMR treated as part of the MARS registry. The authors reported similar rates of acute procedural success for FMR (95.5%, n=84) and DMR (92%, n=69) (p=0.515).

The 30-day mortality rate for FMR and DMR was similar at 4.5% and 6.7% respectively (p=0.555). Thirty-day MAE rate was 9.2% for FMR and 14.7% for DMR (p=0.281). Both FMR and DMR patients achieved significant improvements in MR severity and NYHA class after 30 days. However, a significantly greater reduction in left ventricular end-diastolic diameter and end systolic diameter was observed in DMR compared to FMR.

Overall, results from the MARS registry demonstrate that the MitraClip therapy is effective in reducing mitral regurgitation and has favorable short-term safety outcomes in both FMR and DMR patients.

TVT Registry

The Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry is a joint initiative of the STS and the ACC. The goals of the registry are to serve as a platform for: 1) device and procedural surveillance; 2) quality assurance and improvement initiatives; and 3) efficient conduct of studies that will speed United States access to new devices and support the expansion of device labeling through evidence development.

Centers that participate in the TVT Registry collect data on demographics, morbidities, functional status, quality of life, hemodynamic status, procedural details, and outcomes (post-operative, 30-day, and 1-year). The ACC National Cardiovascular Data Registry data warehouse and the Duke Clinical Research Institute Data Analysis Center both implement data quality checks, including feedback reports and checks on data range and consistency.

Initial Experience (Nov 2013 – Aug 2014)

The initial experience with commercial transcatheter mitral valve repair in the United States was first published by Sorajja et al.⁵⁶ in 2016. A total of 564 patients were entered into the transcatheter mitral leaflet clip (TMC) module of the TVT registry between November 2013 to August 2014. Approximately 70% of patients were enrolled at centers with pre-commercial experience. Median age of the patients was 83 years, 56% were male. NYHA functional class was III or IV in 86.0%; 292 patients (60.5%) had been hospitalized for heart failure in the year prior to the MitraClip procedure. The median STS-PROM scores for MV repair and MV replacement were 7.9% (IQR: 4.7% to 12.2%) and 10.0% (IQR: 6.3% to 14.5%), respectively.

Consistent with the commercial indication for the MitraClip System, the vast majority (85.5%) of patients had degenerative MR, 9.2% had functional MR, and 5.1% had mixed etiology. However, contrary to the EVEREST studies, implanting physicians were given greater discretion in the treatment of mitral valve

⁵⁵ Tay E, Muda N, Yap J, Muller DW, Santoso T, Walters DL, Liu X, Yamen E, Jansz P, Yip J, Zambahari R, Passage J, Ding ZP, Wang J, Scalia G, Soesanto AM, Yeo KK. The MitraClip Asia-Pacific Registry: Differences in Outcomes between Functional and Degenerative Mitral Regurgitation. *Catheter Cardiovasc Interv.* 2016; 87:E275-281.

⁵⁶ Sorajja P, Mack M, Vemulapalli S, Holmes DR, Jr., Stebbins A, Kar S, Lim DS, Thourani V, McCarthy P, Kapadia S, Grayburn P, Pedersen WA, Ailawadi G. Initial Experience with Commercial Transcatheter Mitral Valve Repair in the United States. *J Am Coll Cardiol.* 2016; 67:1129-1140.

pathologies. As such, an important proportion (37.8%) of patients had significant left ventricular dilation (end-systolic dimension ≥ 40 mm), baseline mean mitral gradient ≥ 5 mm Hg (8.0%), and MV area was < 4 cm² (19.7%). Moderate and severe tricuspid regurgitation was present in 35.1% and 15.1% of patients at baseline, respectively.

The MitraClip implant rate was 96.8% with most devices implanted in the A2-P2 region (78.4%). MR reduction to $\leq 2+$ was achieved in 93.0% of patients, while MR grade $\leq 1+$ occurred in 63.7%. Three patients (0.5%) required conversion to open cardiac surgery, and 13 (2.3%) in-hospital deaths were observed. The incidence of in-hospital stroke was 1.2%, while major bleeding (VARC-2 criteria) occurred in 3.9%. Six (1.1%) patients had a single leaflet device attachment (SLDA), and 2 (0.4%) patients had a device embolization. Overall, procedural success, defined as a reduction to moderate or less MR in the absence of cardiac surgery or in-hospital mortality, occurred in 90.6% of patients. The median length of hospital stay post-procedure was 3 days and a majority (84%) of patients were discharged home.

The 30-day mortality rate in the TVT Registry was 5.8%. Stroke at 30 days occurred in a total of 8 patients (1.8%). The 30-day incidence of life-threatening or disabling bleeding (VARC-2 criteria) was 2.6%. A total of 13 (3.1%) patients were re-hospitalized for heart failure within 30 days post-procedure.

Variables with univariate association for reduction in MR $\leq 2+$ were end-diastolic dimension, baseline MR severity, A2-P2 location of clip implantation, and institutional case volume. MitraClip device implantation at A2-P2 remained significant in multivariate models.

Reduction to MR grade $\leq 2+$ was similar at sites with and without precommercial experience (93.8% vs. 91.1%, $p=0.26$), though reduction to MR grade $\leq 1+$ was more common at pre-commercial sites (66.5% vs. 57.4%, $p=0.04$).

Preliminary outcomes from the TVT Registry show that the MitraClip devices is predominantly used in a population of patients at prohibitive surgical risk with symptomatic severe MR due to degenerative disease. Safety and efficacy outcomes of the MitraClip in a commercial setting in the United States were comparable with pre-approval research studies and other commercial registries.

1-Year Outcomes (Nov 2013 – Sep 2015)

In a subsequent report, Sorajja et al.⁵⁷ updated previously published data on acute procedural success and extended the evaluation of these patients to 1-year follow-up. This expanded cohort includes all patients who underwent commercial therapy with the MitraClip System since initial U.S. Food and Drug Administration approval and who were enrolled in the TVT registry through September 1, 2015.

Procedural and in-hospital outcomes were determined from data in the TVT Registry. For clinical events after hospital discharge (i.e., 30-day and 1-year outcomes), data from CMS administrative claims were used via linkage of the clinical records of the TVT registry to Medicare administrative claims data using direct patient identifiers.

Primary outcomes were death, re-hospitalization for heart failure, and the combined endpoint of death or heart failure re-hospitalization within 1 year.

⁵⁷ Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR Jr, Stebbins A, Kar S, Thourani V, Ailawadi G. Outcomes With Transcatheter Mitral Valve Repair in the United States: An STS/ACC TVT Registry Report. *J Am Coll Cardiol.* 2017;70(19):2315-2327.

A total of 2,952 patients were enrolled between November 2013 and September 2015 at 145 clinical sites in the U.S. Patients were elderly with a median age of 82 year; 56% were male. At baseline, 85% were symptomatic with NYHA functional class III or IV. Overall, the median (IQR) STS-predicted risks of mortality for MV repair and MV replacement were 6.1% (3.7% to 9.9%) and 9.2% (6.0% to 14.1%), respectively.

Degenerative MR etiology was present in a majority (85.9%) of patients, whereas functional MR was noted in 17.5% (FMR only 8.6%; mixed etiology 8.9%). Ninety-three percent (93%) of patients presented with 3+ or 4+ MR at baseline. Significant left ventricular dilation (end-systolic dimension ≥ 40 mm) was present in 32.2%. The median LVEF was 55% and 35.4% of the patients had an LVEF $< 50\%$. Baseline mean mitral gradient was ≥ 5 mm Hg in 9.2%, and the MV area was < 4 cm² in 20.5%. Severe tricuspid regurgitation was present in 16.0% of the patients.

The MitraClip was predominantly implanted in the A2-P2 region (82.8% of cases). MR reduction to $\leq 2+$ was achieved in 93.0% of patients, while MR grade $\leq 1+$ was achieved in 61.8%. Single-leaflet device attachment occurred in 1.5% of treated patients. There were 4 reported cases of device embolization (0.1%). Major or life-threatening bleeding (VARC-2 criteria) occurred in 3.9%. The rates of stroke (0.4%) and myocardial infarction (0.1%) were both low. Twenty patients (0.7%) had in-hospital conversion to open cardiac surgery. Overall in-hospital mortality was 2.7%. The median length of hospital stay was 2 days and a majority (85.9%) of the treated patients were discharged directly home.

A total of 1,867 patients (63.2%) from 139 hospitals had records that could be linked to CMS administrative claims. Patients with linked CMS claims data tended to be older, had a lower rate of comorbidities such as diabetes and prior myocardial infarction, and were less likely to have functional MR. However; the STS-predicted risks of operative mortality for MV repair and MV replacement were higher in patients with linked CMS claims data compared to those without linked CMS claims data.

In this cohort, 30-day mortality, including in-hospital events, was 5.2% and the rate of re-hospitalization for heart failure was 4.9%. A majority (95.5%) of patients were discharged from hospital with MR $\leq 2+$, alive and free from MV surgery at 30 days.

One-year mortality in patients with linked CMS claims data was 25.8% and the rate of re-hospitalization for heart failure at 1 year was 20.2%. The combined endpoint of death or heart failure re-hospitalizations at 1 year occurred in 37.9% of the patients. These endpoints were lower for patients who had degenerative MR etiology (24.7%, 20.5%, and 35.7%, respectively) compared to those who had functional MR etiology (31.2%, 32.6%, and 49.0%, respectively).

The subgroup of patients with severe tricuspid regurgitation also had significantly worse outcomes, with 1-year cumulative incidences of 38.5%, 31.5%, and 54.3% for death, heart failure re-hospitalization, and the combined endpoint of death and heart failure re-hospitalization, respectively.

Similarly, a graded effect was noted when comparing cumulative incidence of death and the combined endpoint of death or heart failure re-hospitalization at 1 year by discharge MR. As expected, better outcomes were observed in patients discharged with MR $\leq 1+$ (21.7% and 35.7%, respectively) compared to those discharged with MR 2+ (29.2% and 39.2%, respectively), and MR $\geq 3+$ (48.9% and 54.4%, respectively).

At 1 year, 6.2% of patients with linked CMS claims data required a second MitraClip procedure. The cumulative rate of stroke was 2.7%.

Variables associated with mortality or re-hospitalization for heart failure after multivariate adjustment were increasing age, lower baseline LVEF, worse post-procedural mitral regurgitation, moderate or severe lung disease, dialysis, and severe tricuspid regurgitation.

Based on these data, the authors conclude that the MitraClip procedure is being performed effectively and safely for severely symptomatic patients with MR and prohibitive surgical risk in the United States and contend that the observed mortality and re-hospitalizations for heart failure are related to age and associated with decreased LVEF, functional MR, severe tricuspid regurgitation, moderate or severe lung disease, and post-procedural residual MR.

Non-EVEREST Criteria

Patients treated with the MitraClip device as part of the EVEREST program had to meet specific anatomic inclusion criteria. These criteria, included a regurgitant jet origin associated with the A2 to P2 segments of the mitral valve and, for patients with functional MR, a coaptation length of at least 2 mm, a coaptation depth of no more than 11 mm, and for patients with leaflet flail, a flail gap <10 mm and a flail width <15 mm. In addition, leaflet anatomy which may preclude device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR were excluded. This may include:

Evidence of calcification in the grasping area of the A2 and/or P2 scallops

Presence of a significant cleft of A2 or P2 scallops

More than one anatomic criteria dimensionally near the exclusion limits

Bileaflet flail or severe bileaflet prolapse

Lack of both primary and secondary chordal support

In a real-world clinical setting, experienced implanters have started treating more complex mitral valve anatomies, often falling outside of the traditional EVEREST criteria. In a recent publication, Lesevic et al.⁵⁸ analyzed patients treated with the MitraClip device according to the presence or absence of EVEREST inclusion criteria and compared the procedural success and long-term outcomes, repair durability, and prognostic factors.

Consecutive patients treated with the MitraClip device at the German Heart Center in Munich between September 2009 to July 2012 were included. All patients underwent 2D transthoracic and 2D and 3D transesophageal echocardiography before intervention to assess valve morphology, MR severity, and suitability for the MitraClip procedure. Patients were assigned to the EVEREST (N=59) or non-EVEREST (N=75) groups depending on whether they would have met the eligibility criteria for the EVEREST II trial.

In this study, key reasons for not meeting the EVEREST criteria included LVEF <25 % and/or LVESD >55 mm in 24% of patients, coaptation length <2 mm in 19%, main pathology in P1- and/or A1-segment (prolapse +/- flail) in 15%, main pathology in P3- and/or A3-segment (prolapse +/- flail) in 12%, flail gap >10 mm in 8%, and flail width >15 mm in 4%.

Baseline characteristics were comparable between the two groups. Functional MR etiology was present in 39% and 41% of EVEREST and non-EVEREST groups, respectively. Both groups were high risk for surgery with STS mortality scores of 10.7% and 10.1% for EVEREST and non-EVEREST patients, respectively.

⁵⁸ Lesevic H, Karl M, Braun D, Barthel P, Orban M, Pache J, Hadamitzky M, Mehilli J, Stecher L, Massberg S, Ott I, Schunkert H, Kastrati A, Sonne C, Hausleiter J. Long-Term Outcomes after MitraClip Implantation According to the Presence or Absence of EVEREST Inclusion Criteria. *Am J Cardiol.* 2017; 119:1255-1261.

One hundred and thirty-four (134) patients were treated with the MitraClip device. Acute procedural success was achieved in 95.5% of patients with no difference between EVEREST (97%) and non-EVEREST (95%) patients. There was no statistical difference in the number of device implanted between the two groups. A similar mean acute MR reduction was achieved in both groups (-2.3 ± 0.9 vs -2.2 ± 1 , respectively; $p=0.497$).

During a mean follow-up of 3.5 years, 32 deaths were reported, including 5 occurring during the hospital stay post-index procedure. Survival rates were similar between EVEREST and non-EVEREST patients ($p=0.656$). Recurring MR $\geq 3+$ was more frequent in non-EVEREST patients than in EVEREST patients (28% vs 45%; $p=0.066$). Re-interventions for recurring MR were more frequently required in non-EVEREST patients than in EVEREST patients, including second MitraClip device interventions (2% vs 13%; $p=0.085$) and mitral valve surgeries (9% vs 28%; $p=0.047$). Of the 21 patients requiring re-intervention in both groups, 17 (81%) had degenerative MR. Flail width was found to be an independent predictor for re-intervention, whereas flail gap ≥ 10 mm displayed a strong trend (flail width: adjusted HR 11.2, 95% CI 2.6 to 48.3; $p=0.001$; flail gap: adjusted HR 3.1, 95% CI 0.9 to 11.5; $p=0.077$). When entering the variables into logistic regression analyses for identifying independent factors associated with MR $\geq 3+$ at follow-up, only flail gap ≥ 10 mm displayed a trend ($p=0.082$).

At last available follow-up (median of 381 days), both groups achieved significant reduction in MR severity over baseline. Similarly, NYHA functional class improved in both EVEREST and non-EVEREST patients from baseline to longest available follow-up (median of 652 days). Finally, both groups experienced clinically and statistically significant improvements in 6-minute walk distance from baseline to the latest follow-up visit, with no difference between EVEREST and non-EVEREST groups.

This data show that significant reduction of MR severity can be achieved in patients who do not meet the EVEREST II trial criteria. Nevertheless, non-EVEREST patients were significantly more likely to require re-intervention for recurring MR due in part to more complex mitral valve pathologies including flail width >15 mm and flail gap ≥ 10 mm. These results also support the assumption of previous studies that selected patients, especially with secondary MR, can benefit from percutaneous treatment with the MitraClip device.

In contemporary clinical practice, a small, but non-negligible proportion of patients with severe MR present complex mitral valve pathologies which would normally be excluded based on a strict application of EVEREST II anatomical criteria. Success achieved with the MitraClip device in these patients and physician interest in using the clip for treating complex valve anatomies forms the rationale for the MitraClip® EXPAND Study.

APPENDIX V: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Clinical Project Manager for the study.

APPENDIX VI: CONTACT INFORMATION

A list of site contacts can be obtained upon request from the Clinical Project Manager for the study.

APPENDIX VII: FORESEEABLE ADVERSE EVENTS

Please see device instructions for use regarding potential adverse events.

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]