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EXPAND G4
MitraClip EXPAND G4
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Version [C]
Date: 04-NOV2020

Sponsor	Abbott 3200 Lakeside Dr Santa Clara, CA 95054

Clinical Investigation Plan

MitraClip EXPAND G4

A Post-Market Study Assessment of the Safety and Performance of the MitraClip™ G4 System

[redacted]

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PROTOCOL SUMMARY FOR MITRACLIP EXPAND G4 STUDY – PHASE I AND II

Version	[redacted]
Date	[redacted]
Protocol Name and Number	[redacted]: MitraClip EXPAND G4 Study
Sponsor	Abbott 3200 Lakeside Drive, Santa Clara, CA 95054
Title	A Post-Market Study Assessment of the Safety and Performance of the MitraClip G4 System
Objectives	The primary objective of this study is to evaluate the safety and performance of the MitraClip G4 System in a post-market setting.
Devices	MitraClip G4 NT System MitraClip G4 XT System MitraClip G4 NTW System MitraClip G4 XTW System
Targeted Number of subjects	Up to [redacted] subjects at up to [redacted] sites in the [redacted]. Phase I: [redacted] subjects at up to [redacted] sites in the US followed through 30 days ([redacted]). Phase II: [redacted] subjects at up to [redacted] sites in the [redacted] followed through 5 years.
Subject Visit Schedule	**Clinical Visits:** Baseline, Discharge, 30 days, 1 year, 2 year, 3 year, 4 year, 5 year **Phone Call:** 6 months
Endpoints	***Safety*** • 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* ***Performance*** • Mitral Regurgitation (MR) Reduction to ≤2+ at 30 days **Procedure endpoints:** • Acute Procedural Success (APS) • Acute Device Success • 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

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	• Use of Controlled Gripper Actuation
	• In-hospital MAE defined as the number of MAEs that occur prior to discharge from hospitalization in which MitraClip Procedure was performed
	
	Clinical endpoints (*Discharge, 30 day, 6 month, 1, 2, 3, 4, 5 year)):*
	• All-cause Mortality
	• Heart Failure Hospitalization
	• Occurrence of AE
	• Device-Related Complications
	  ○ Mitral valve stenosis
	  ○ Single Leaflet Device Attachment (SLDA)
	  ○ Device Embolization
	  ○ 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
	• MR Reduction to ≤1+ ***(Discharge, 30 day, 1 year, 5 year)***
	• MR Reduction to ≤2+ ***(Discharge, 30 day, 1 year, 5 year)***
	• New York Heart Association (NYHA) functional class improvement
	• Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)
	• 6 minutes walk distance (6MWD)
	
	Echocardiographic endpoints:
	(Baseline, Discharge, 30 day, 1 year, 5 year):
	• MR Severity Grade
	• Effective Regurgitant Orifice Area (EROA) as measured by PISA method (Baseline only)
	• Coaptation Measures (depth/length) (Baseline only)
	• *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) (Baseline only)
	• Grasping Area Anatomy (measure cleft or scallop if significant)
	• Assess chordal support (Baseline only)
	• Regurgitant Jet(s) Position and Quantity (Baseline only)
	• Tricuspid Regurgitation (TR) Severity: None, Mild, Moderate or Severe

Inclusion Criteria	1. Subjects scheduled to receive the MitraClip per the current approved indications for use

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	2. Subjects who give consent for their participation
Exclusion Criteria	1. Subjects participating in another clinical study that could impact the follow-up or results of this study.
Abbott Medical Expert	[redacted] Global Medical Affairs Director, Mitral and Tricuspid Transcatheter Interventions, Abbott Structural Heart [redacted]
CIP Author	[redacted] Associate Director Clinical Science, Abbott Structural Heart

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
Signature:
Date:

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NATIONAL COORDINATING CLINICAL INVESTIGATOR / STUDY PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

[Coordinating Clinical Investigator / Study Principal Investigator]

Printed name:
Signature:
Date:

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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) or Internal Review Boards (IRBs) of the respective study site and by the applicable regulatory authorities.

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1.0 INTRODUCTION

This clinical study protocol defines the MitraClip EXPAND G4 study being conducted to confirm the safety and performance of the MitraClip G4 System in a post-market setting. This Post-market study will be conducted on commercial cases conducted with the approved MitraClip G4 System.

The MitraClip® System received Conformité Européene approval (CE Mark) in 2008 and US Food and Drug administration (FDA) Approval in 2013 and 2019 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 [redacted] patients in clinical trials and more than [redacted] patients in worldwide use to date. Abbott is now introducing the next generation MitraClip G4 System. This new system has three important advancements over the previous MitraClip Systems:

- Introduction of two new clip sizes: NTW and XTW
- Incorporation of the option to grasp leaflets simultaneously or independently, i.e., controlled gripper actuation (CGA)
- Integration of a continuous left atrial pressure (LAP) monitoring from the Steerable Guide Catheter

The MitraClip EXPAND G4 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 G4 System. The prospectively generated data in this study will be used to evaluate device outcomes and to evaluate the clip selection and leaflet grasping recommendations identified by the MitraClip G4 Advisory Board (**Appendix I**) in contemporary real-world settings. 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 G4 Study will become part of the MitraClip G4 Post Market Clinical Follow-up (PMCF) Study (**Appendix II**). Data from the MitraClip G4 PMCF Study will be used to fulfill the regulatory requirement for PMCF associated with the CE mark approval of the MitraClip G4 System.

The next generation MitraClip G4 system received FDA approval in July 2019 for use in the United States, was authorized by Health Canada in July 2019, received approval in Japan in June 2020, and received CE Mark in September 2020. The MitraClip EXPAND G4 Study will be conducted on commercial MitraClip G4 System that have received approval in the local geography as required.

[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

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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 G4 System. The study is designed in two phases:

- Phase I: Clinical and echocardiographic outcomes data was collected from approximately [redacted] subjects enrolled at approximately [redacted] sites in the United States with the goal of evaluating the early safety and procedural outcomes associated with the MitraClip G4. The follow up duration was 30 days. Phase I was completed [redacted].

- Phase II: Up to [redacted] post-market, consented patients will be treated with a MitraClip G4 device according to local guidelines and IFU from the Europe, the United States, Canada and Japan will be included in the analysis for The MitraClip EXPAND G4 Study. Follow-up echocardiograms will be collected at Discharge, 30 days and 1 year and 5 year at post-procedure visits. Additional clinical follow-up visits will be at 6 months (phone call), 2, 3, 4 year (office visits). Cardiovascular adverse events will be reported through 5 years to confirm safety of the MitraClip G4 System. The current protocol describes the design of the EXPAND G4 Phase II post-market study.

1.2 Study Objective

The primary objective of this study is to assess the safety and performance of the MitraClip G4 System within a contemporary real-world setting.

2.0 BACKGROUND and RATIONALE

2.1 Regulatory History

In 2008, based upon data from the EVEREST studies, the MitraClip® received CE mark approval for commercial use in Europe. 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 primary MR who are at prohibitive risk for surgery. In March 2019, FDA expanded the indication to treat patients with heart failure symptoms and moderate-to-severe or severe secondary mitral regurgitation despite being treated with optimal medical therapy, based on the landmark COAPT study results. The current iteration of the device: MitraClip G4, which was the subject of this clinical study, was approved by FDA in July 2019, approved in Canada in July 2019, approved in Japan in June 2020, and received CE Mark in September 2020.

2.2 MitraClip® Post-Market Clinical Studies

In the time since these approvals, a number of post-market clinical studies have been conducted on the MitraClip. All 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**.

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Table 1. Summary of Post-Market MitraClip® Studies

Study Reference	Study Design	Study Population	Study Outcome
Franzen et al.[3] 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[4] (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[5]
Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation GRASP Registry[6]	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. Several TRAMI reports have been published [7,8]	828 prospective patients at 21 sites (from the largest publication[9]) 70%FMR 94% Severe MR	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

[3] 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.

[4] 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.

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

[6] Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistritto 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.

[7] 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.

[8] 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.

[9] 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.

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The Transcatheter Valve Treatment Sentinel Pilot Registry[10]	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.[11] -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)
A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip® Devices (EXPAND)[12]	Prospective, Multi-center, Single Arm, International, Post-Market, Real World, Observational Study Conducted in United States and Europe.	~1000 patients MR ≥3+ Euroscore II : 8.1 ± 8.0 (539)	Acute procedure success rate 92.9% 30 day major adverse event rate was very low. MR ≤ 2+ at 30 day at 90.1% in primary MR patients and 96.3% in secondary MR patients.

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.[13] analyzed the outcomes of patients enrolled in the GRASP registry according to baseline echocardiographic criteria. A total of 78 patients that met EVERST criteria ($EVEREST_{on}$) were compared to 93 patients that did not meet EVEREST Criteria ($EVEREST_{OFF}$) which included 35 patients with LVEF ≤25%, 28 patients with LV end systolic diameter >55 mm, 34 patients with coaptation depth ≥11 mm,

[10] Therapy in Contemporary Clinical Practice: Results from the German Transcatheter Mitral Valve Interventions Registry. *Eur Heart J*. 2016; 37:703-712.
[11] 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.
[12] von Bardeleben RS et al., Contemporary, real-world, clinical outcomes with the next generation MitraClip™ (NTR/XTR) System: Results from the 1000+ patient global EXPAND Study. Presentation, ESC 2019.
[13] 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.

and 10 patients with a flail width ≥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 ≥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 ≤2+.

In more recent 2016 publication, Lesevic et al.[14] 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 ≥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 ≥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).

In addition, Abbott has initiated a large scale observational study (1000 patients) in US and EU (EXPAND) to evaluate the safety and performance of the MitraClip NTR/XTR system. The 30 day study outcomes were recently reported in ESC 2019[15]. The acute procedure success rate was 92.9% (962/1035) and 30 day major adverse event rate was very low. MR ≤ 2+ at 30 day was achieved at 90.1% in primary MR patients and 96.3% in secondary MR patients. This study also characterized the baseline mitral valve anatomic features (assessed by the echo core-lab) associated with NTR and XTR clip selection. It was identified that MitraClip XTR (compared to NTR) was more often used in Primary MR in subjects with larger gaps. For secondary MR patients, XTR was used when there was significant leaflet tethering, particularly in the P2/P3 locations. Data presented in EuroPCR 2020[16] showed that MR reduction with XTR clip size was more favorable in PMR subjects with more complex MV anatomies, larger prolapse, smaller ventricles and more severe MR. and thereby demonstrating the utility of XTR Clip in tailoring the therapy to individual's MV anatomy.

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

[14] 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.

[15] von Bardeleben R. S. et al. Contemporary, real-world, clinical outcomes with the next generation MitraClip (NTR/XTR) System: Results from the 1000+ patient global EXPAND Study. European Society of Cardiology (ESC) Congress 2019.

[16] Maisano F. et al. Clip Selection Strategy and Outcomes with MitraClip™ (NTR/XTR): Evidence-Based Recommendations from the Global EXPAND Study. EuroPCR e-Congress 2020.

the mitral valve anatomical characteristics that may benefit most from the attributes of this device iteration (i.e. wider arms on the implant and independent leaflet grasping feature). This study will also prospectively collect data on utility of integrated LAP monitoring during MitraClip procedure to improve the procedural and clinical outcomes. These are the basis for the MitraClip EXPAND G4 Study.

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

2.3 Rationale for Conducting this Study

The primary objective of the MitraClip EXPAND G4 study is to confirm the safety and performance of the MitraClip® G4 System 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 G4 Systems. A subset of patients will be analyzed as part of the MitraClip G4 PMCF Study (Appendix II) to fulfill this requirement.
- The recent advancements with wider clip arms on MitraClip NTW and XTW, and the controlled gripper actuation (CGA) feature of the MitraClip G4 Systems may offer an advantage in leaflet approximation of certain mitral valve anatomies; this study will help to identify populations that can benefit most from these next generation MitraClip Systems.
- This study will generate prospective data to evaluate the clip selection and leaflet grasping technique recommendations generated by the MitraClip G4 Advisory board and provide validation through real-world outcomes.

2.4 Summary of Device

2.4.1 Name of the Device

Patients will be treated with MitraClip G4 System as part of this study after required approval of the study is obtained.

2.4.2 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.

2.4.3 Description of the Device

[redacted]

FIGURE 1: MitraClip® G4 System

3.0 STUDY FLOW and FOLLOW-UP SCHEDULE

3.1 Number of Subjects to be Enrolled

In accordance with ISO 14155, subjects who have provided written informed consent are 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 for adverse events. Following the consent, if thrombus is identified at baseline and medically treated and resolved at a later date, a patient may be re-consented for the EXPAND G4 Study if they are eligible for a new attempted MitraClip procedure.

Up to [redacted] consented subjects with confirmation of no thrombus who have a MitraClip procedure attempted will be included for analysis in the MitraClip G4 EXPAND Study. Phase II study will include [redacted] subjects. The Study will be conducted at a maximum of [redacted] centers in the EU, the US, Canada and Japan. A site maximum of [redacted] subjects will be enforced so that no site will be permitted to submit data for more than [redacted] of the study population.

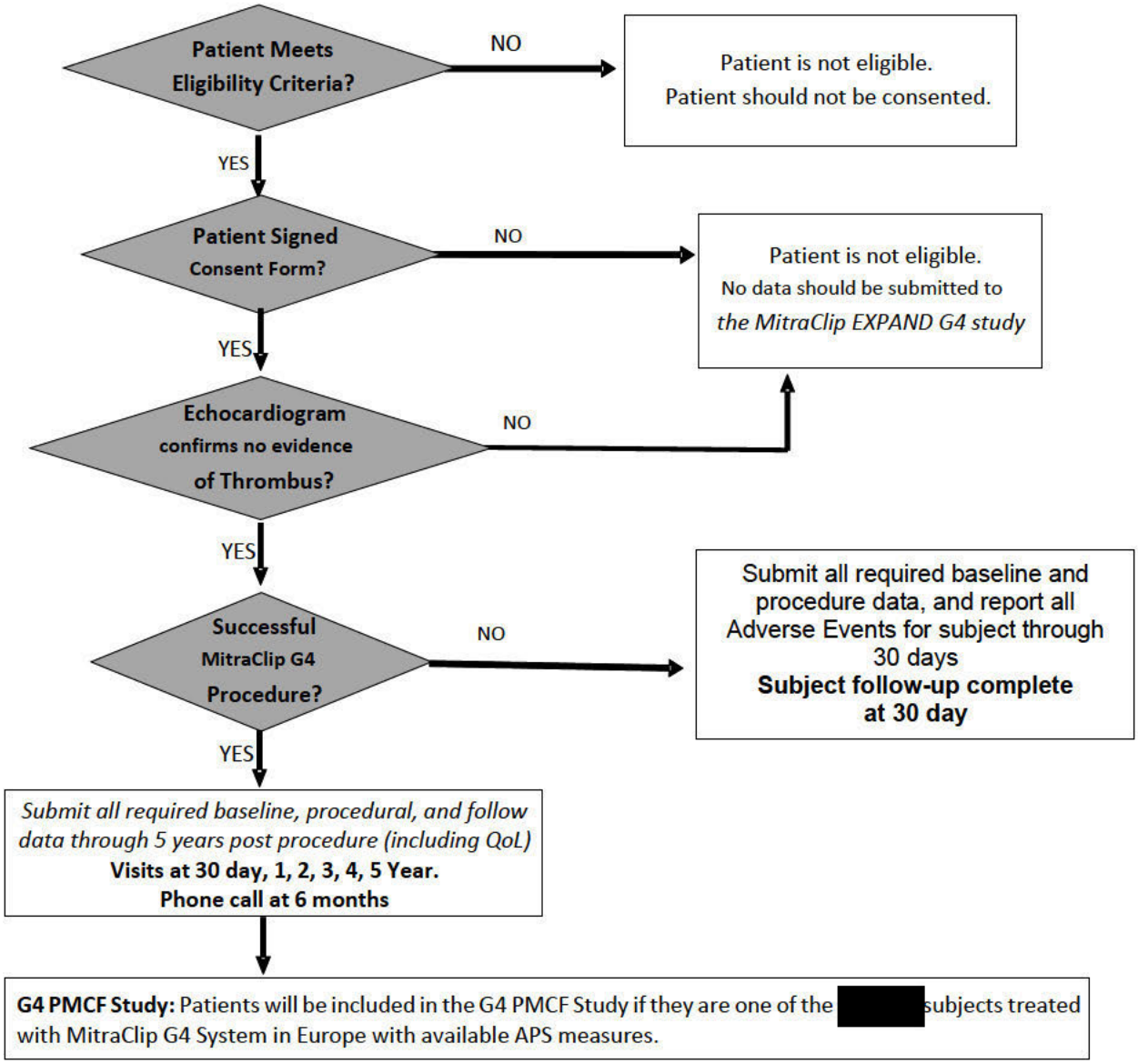

FIGURE 2: Schematic for Study Inclusion and Flow

3.2 Study Flow and Follow up Schedule

Consecutive eligible patients that present for MitraClip procedure should be consented for the MitraClip EXPAND G4 Study. Patients are included in the analysis upon completion of MitraClip G4 procedure.

Follow-up data on clinical assessment should be submitted at ischarge, 30-day visit, 6-month phone call, 1 year, 2 year, 3 year, 4 year and 5 year visits. Echocardiograms are required to be submitted for the baseline, discharge, 30-day and 12-month and 5 year time points. All Echocardiograms conducted by the site during the study period (required by protocol or not) will be submitted to the Sponsor (see **Table 2**). Section 6.4 of this protocol provides more detail on follow-up visits.

The first [redacted] subjects treated with the MitraClip G4 in the MitraClip EXPAND G4 Study in Europe with evaluable acute procedural success (APS) data will be included in the G4 PMCF Study as described in Appendix II. Subjects with evaluable echocardiograms may be selected for a more detailed assessment by an independent core lab.

A schematic of the study flow is shown in **Figure 2.**

3.3 Early Termination of the Clinical Study

No formal statistical rule for early termination of the MitraClip EXPAND G4 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:

- 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 Internal Review Board/Ethics Committee (IRB/EC).

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.

- Performance
  The assessment of performance measures will include all data reported at 30-day visits for this study.

[redacted]

MR Reduction to ≤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), or myocardial perforation) through discharge.
- 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.
- Use of Controlled Gripper Actuation (CGA)
- Use of Left Atrial Pressure (LAP) Monitoring
- Number of Attempted Grasps defined as the number of attempts to stabilize leaflets by the open Clip
- Device-Related Complications defined as the occurrence of one of 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
  - 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 Major Adverse Events (MAE) defined as the number of MAEs that occur prior to discharge from hospitalization in which MitraClip Procedure was performed.

4.3 Clinical Measures

(Discharge, 1, 6 and 12 months, and 2, 3, 4, 5 years):

- All-cause Mortality
- Heart Failure Hospitalization
- MAE as defined above
- Device-Related Complications defined above
  MR Reduction to ≤1+ ***(Discharge, 1, 12 months, and 5 years)***
- MR Reduction to ≤2+ ***(Discharge, 1, 12 months, and 5 years)***

4.4 Functional Improvement Measures

(Baseline, Discharge, 12 months, and 2, 3, 4, 5 years):

- New York Heart Association (NYHA) functional class improvement
- Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- 6 minutes walk distance (6MWD)

4.5 Echocardiographic endpoints:

(Baseline, Discharge, 1, 12 months, and 5 years):

- MR Severity Grade
- Effective Regurgitant Orifice Area (EROA) as measured by PISA method (Baseline only)
- Coaptation Measures (depth/length) (Baseline only)
  - *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) (Baseline only)
  - *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) (Baseline only)
- Assess chordal support (Baseline only)
- Regurgitant Jet(s) Position and Quantity (Baseline only)
- TR Severity: None, Mild, Moderate or Severe

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This study will include an analysis of all consented subjects who satisfy the inclusion and exclusion criteria and who are treated with the MitraClip G4 System. The study will include approximately [redacted] subjects treated with the MitraClip G4 System that have data available for assessment of APS.

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 EXPAND G4 Study if they are eligible per the inclusion/exclusion criteria.

5.2.2 Informed Consent

Patient Information and Consent Form must receive approval of Sponsor and Ethics Committee (EC) or Internal Review Board (IRB) prior to beginning enrollment into the MitraClip EXPAND G4 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 G4 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) EC/IRB approved informed consent prior to any data is reported into this 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.

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 the EC/IRB, subjects from vulnerable populations may be enrolled in the study. The ISO14155 definition of vulnerable population is as follows: individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response. 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 consented subjects treated commercially with the MitraClip G4 System should be considered for inclusion in the study. All subjects must meet the criteria below before being enrolled into the MitraClip G4 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

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

Per ISO 14155, the patient is considered enrolled upon signing and dating an informed consent for participation. Only subjects that have an attempted MitraClip G4 procedure will be included in this analysis.

5.5 Total Expected Duration of the Study

The time to complete the MitraClip EXPAND G4 study is estimated to be approximately [redacted] years.

5.6 Expected Duration of Each Subject's Participation

The final required visit for subjects in the MitraClip EXPAND G4 Study is at [redacted] year post-procedure. Therefore, the expected duration of participation for subjects is approximately [redacted] years.

5.7 Number of Subjects Required to be Included in the Study

Approximately [redacted] subjects will be included in the MitraClip EXPAND G4 Study.

5.8 Estimated Time Needed to Select this Number

The estimated time to include [redacted] subjects in Phase II is about [redacted] years.

5.9 Subject Discontinuation

Subjects that are consented and receive a MitraClip G4 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 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 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

[redacted]

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.

5.10 Subject 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., 5 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. If a MitraClip procedure is considered appropriate and the patient meets the screening criteria for the study (i.e. 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. 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: demographics, medical history, surgical risk (STS Repair/Replacement Scores and/or EuroSCORE II), MR severity and New York Heart Association (NYHA) Functional Class and KCCQ. If a 6-minute walk test is conducted as standard of care at baseline, these results will be collected in the G4 EXPAND Study.

6.1.2 Pre-treatment Imaging

Pre-Treatment Transthoracic Echocardiogram (TTE) and Transesophageal Echocardiogram (TEE) should be conducted per standard of care for a MitraClip Procedure.

6.2 Index Procedure

All Investigators must read and understand the Instructions for Use (IFU) that accompanies the Device. Handling and preparation of the MitraClip G4 System should be in accordance with the IFU.

The MitraClip procedure should be conducted in accordance with standard of care practice and approved labelling. All consented patients that have a successful or attempted procedure with the MitraClip G4 will be entered into the study.

NOTE FOR U.S. Sites: In order to permit device reimbursement, please enter required data into the TVT Registry per your standard processes for all MitraClip EXPAND G4 cases. The data collected in this registry does not replace the data collected by the TVT Registry (US).

6.3 Post-procedure

Post treatment TTE, Clinical Assessments and Laboratory / Clinical Tests should be conducted prior to discharge per standard of care. Some of the key post-procedure information (the discharge time point) to be reported for this study include: Medical Exam and Reporting of Vitals, length of hospital stay, adverse events, MR severity and NYHA Functional Class.

6.4 Subject Follow-up

Follow-up visits should be conducted per standard of care based on the follow up schedule outcomes in Table 2. During the follow-up period for this study (5 years) any unscheduled echocardiograms, either TEE or TTE, should be submitted.

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, 12-month and 2, 3, 4, 5-year visits. Visit should be scheduled relative to the date of the MitraClip Procedure. If a 6-minute walk test is conducted as standard of care and was conducted at baseline; results for 6-minute walk test at 30 day,12-months and 2, 3, 4, 5-year visits will be collected in the EXPAND G4 Study.

Visits at:

- 30 days (-14 days / +60 days)
- 1, 2, 3, 4, 5 years (- 30 days / +90 days)

Phone call or visit at:

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

Table 2. Clinical Follow-Up Schedule

[redacted]

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

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.

As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:
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.

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 be reported during this study include: all cardiovascular events, events classified as MAEs (as defined in section 4.1) and device-related complications (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 5 year follow up visit. 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 SAE Notification Form will be made available to allow the investigator to report required SAEs in the event the entry cannot be made in the Electronic Data Capture (EDC) System. 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 IRB/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 IRB/EC per the investigative site's local requirements. A device deficiency 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 STATISTICAL ANALYSIS

8.1 Statistical Overview

This is a post-market multicenter study of consecutive consenting patients treated with the MitraClip G4 system at participating centers. The study will enroll approximately [redacted] subjects to collect clinical evidence for the MitraClip G4 system to characterize the use and outcomes associated with the device.

8.2 Analysis Populations

All subjects who signed and dated an Inform Consent Form and were treated with a MitraClip G4 device will be included in the analysis.

8.3 Sample Size Calculations and Assumptions

[redacted]

[redacted]

[redacted]

8.4 Statistical Analyses

[redacted]

8.4.1 Study Endpoint Analyses

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

8.4.2 Handling of Multiplicity Issues

No multiplicity adjustment is needed for this study.

8.4.3 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.

8.5 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.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents in order as required 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

[redacted]

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.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

Sponsor will select investigators qualified by training and experience, to participate in the study of the MitraClip G4 System. 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. Sites will be required to perform some cases with the MitraClip G4 System before participating the MitraClip EXPAND G4 Study.

10.2 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 of the Protocol amendment (administrative changes) or obtaining EC's/IRB'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/IRB 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.

10.3 Training

10.3.1 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; 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.

10.3.2 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.

10.4 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.

10.5 Deviations from Protocol

The Investigator will not deviate from this 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.

10.6 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.

10.7 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/IRB 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.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 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.

11.2 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 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

11.3 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.

11.4 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.

12.0 ETHICAL CONSIDERATION

12.1 Medical Ethics Committee Review

Ethics Committee (EC) or Internal Review Board (IRB) 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 IRB/EC, the Sponsor, and/or the regulatory agencies as needed.

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

13.0 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.

14.0 RISK ANALYSIS

14.1 Anticipated Clinical Benefits

Treatment with the MitraClip has been shown to effectively reduce Mitral Regurgitation in several clinical studies (Table 1 of this protocol). Treatment with the MitraClip G4 System within this study is anticipated to offer this same established benefit. The changes to the MitraClip G4 System were designed to have the same clinical impact with added ease in grasping of the mitral leaflets during the implant procedure. Design validation study indicates that users also responded favorably to the simplified Clip deployment procedure, stating that it is significantly better to the MitraClip NTR/XTR deployment procedure. Users rated leaflet grasping and capture with MitraClip G4 as better than leaflet grasping and capture with MitraClip NTR/XTR. Data from this study may help to further identify benefits of the MitraClip G4 device in improving mitral leaflet grasping and improve clinical outcomes.

14.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Please refer to the approved Instruction for Use for possible adverse events of the MitraClip™ G4 procedure.

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 G4 device as part of this study is identical to treatment with the MitraClip G4 device outside of this study. Participation in the study will not impact the MitraClip G4 procedure or use of the MitraClip G4 System in any way, therefore there is no added procedural risk by participating in this study.

Participation in the study requires submission of data that may or may not be protected heath 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

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.

In the study, the device is required to be used in accordance with the MitraClip® System IFU Contraindications, warnings and precautions will be provided with all devices to be used during this study per the IFU.

14.7 Risk to Benefit Rationale

Subjects participating in this study will be receiving the latest technology in MitraClip. MitraClip has been be safe and effective in over [redacted] patients in clinical trials and more than [redacted] 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 G4 implant within this study are identical to the risks of receiving a MitraClip G4 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 the enrollment of patients treated with the MitraClip G4 System into this study.

Clinical Investigation Plan

APPENDIX I – MITRACLIP G4 CLIP SELECTION AND LEAFLET GRASPING TECHNIQUE RECOMMENDATIONS

[redacted]

Table 3: Clip Size Selection Recommendations for the MitraClip G4 System.

[redacted]

[redacted]

[redacted]

Clinical Investigation Plan

[redacted]

[redacted]

[17] Nishimura RA, Otto CM, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines J Am Coll Cardiol 2014:0735-1097

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Clinical Investigation Plan

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Clinical Investigation Plan

APPENDIX II – MITRACLIP G4 PMCF CLINICAL STUDY PROTOCOL

[redacted]

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10320-1: MitraClip G4 PMCF Study

(sub-analysis of the first [redacted] European subjects in EXPAND G4 Study)

A Post-Market Clinical Follow-up Assessment of the Safety and Performance the MitraClip G4 System

Version Number	[redacted]
Date	November 4, 2020
Planned Number of Sites and Region(s)	[redacted]
Protocol Author	[redacted] Associate Director Clinical Science Abbott Structural Heart

[redacted]

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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.

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PROTOCOL SUMMARY FOR MITRACLIP G4 PMCF STUDY

Protocol Name and Number	[redacted]: MitraClip G4 PMCF Study
Title	Post-Market Clinical Follow up Assessment of the Safety and Performance of the MitraClip G4 System
Objectives	The primary objective of this study to evaluate the safety and performance of the MitraClip G4 System in a post-market setting.
Devices	MitraClip G4 NT System MitraClip G4 XT System MitraClip G4 NTW System MitraClip G4 XTW System
Targeted Number of subjects	A minimum of [redacted] subjects treated in Europe
Subject Visit Schedule	**Clinical Visits:** Baseline, Discharge, 30 days, 1, 2, 3, 4, 5 years **Phone Call:** 6 Months
Primary Endpoint	*Safety and Effectiveness* 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.
Clinical Endpoints	• 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 • MR Severity (evaluated at Discharge, 30 days, 1 year and 5 years) • Device Related Adverse Events (including Mitral valve stenosis, device embolization, Single Leaflet Device Attachment (SLDA), 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 • Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) • 6 minute walk distance (6MWD)
Inclusion Criteria	1. Subjects scheduled to receive the MitraClip per the current approved indications for use 2. Subjects who give consent for their participation

[redacted]

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

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1.0 INTRODUCTION

This clinical study protocol defines the MitraClip G4 post-market clinical follow-up (PMCF) study being conducted to confirm the safety and performance of the MitraClip G4 in a post-market setting. The MitraClip G4 System introduces three important advancements over the previous MitraClip System by (i) two new clip sizes: NTW and XTW, (ii) the option to grasp leaflets simultaneously or independently, i.e., controlled gripper actuation (CGA), and (iii) continuous left atrial pressure (LAP) monitoring integrated into the Steerable Guide Catheter. These advancements are intended to assist physician during the procedure to achieve improved leaflet grasping. The MitraClip System has been implanted over [redacted] subjects world-wide and shown safe and effective for the treatment of patients with significant mitral regurgitation (MR) through extensive published clinical evidence (see section 2.1). MitraClip G4 PMCF study aims to generate further clinical evidence to continue to support safety and performance of the MitraClip G4 System.

This PMCF study will be conducted on commercial MitraClip G4 devices following the CE Mark approval 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 G4 System by comparing the rate of acute procedural success after treatment with the MitraClip G4 to an expected rate based on historical MitraClip data.

A minimum of [redacted] post-market, consecutive, consented, patients treated with the MitraClip G4 device in the EU will be included for analysis into the MitraClip G4 PMCF study. Clinical follow-up visits will be requested at Discharge, 30 days, 1, 2, 3 4, 5 years post-procedure. An additional clinical follow-up phone call will be at 6 months. Reported adverse events through 5 years 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 G4 System in a post-market setting. This study will be conducted in accordance with post market clinical follow-up requirements.

2.0 BACKGROUND AND RATIONALE

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.

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ACCESS-EU[18] 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 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 registry[19]. 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[20,21]. The largest prospective cohort was described by Puls

[18] 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.

[19] Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistritto 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.

[20] 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.

[21] 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.

et al.[22]. 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 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 ≤2+ was achieved in 98.2% of patients post-procedure with no difference between MR etiologies. At 1-year, MR was reduced to ≤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.

In addition, Abbott has initiated a large scale observational study ([redacted] patients) in US and EU (EXPAND) to evaluate the safety and performance of the MitraClip NTR/XTR system. The 30 day study outcomes were recently reported in EuroPCR. The acute procedure success rate was 92.9% (962/1035) and 30 day major adverse event rate was very low. MR ≤ 2+ at 30 day was achieved at 90.1% in primary MR patients and 96.3% in secondary MR patients. This study also characterized the baseline mitral valve anatomic features (assessed by the echo core-lab) associated with NTR and XTR clip selection. It was identified that MitraClip XTR (compared to NTR) was more often used in Primary MR in subjects with larger gaps. For secondary MR patients, XTR was used when there was significant leaflet tethering, particularly in the P2/P3 locations.

The totality of post-market clinical evidence supports the use of the MitraClip System for the treatment of MR. The MitraClip G4 PMCF Study will assess the safety and performance of the next generation MitraClip G4 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 G4 System. The primary analysis will be conducted using the endpoint of Acute Procedural

[22] 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.

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 G4 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 G4 System as part of this study after required approval of the study 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

[redacted]

[redacted]

FIGURE 1: MitraClip® G4 System

3.0 STUDY FLOW AND 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 G4 the subject will be included in this PMCF analysis. A minimum of [redacted] commercial MitraClip G4 patients will be analyzed at a maximum of [redacted] centers in the EU as part of this PMCF study. A schematic of the study flow is shown in **Figure 2.**

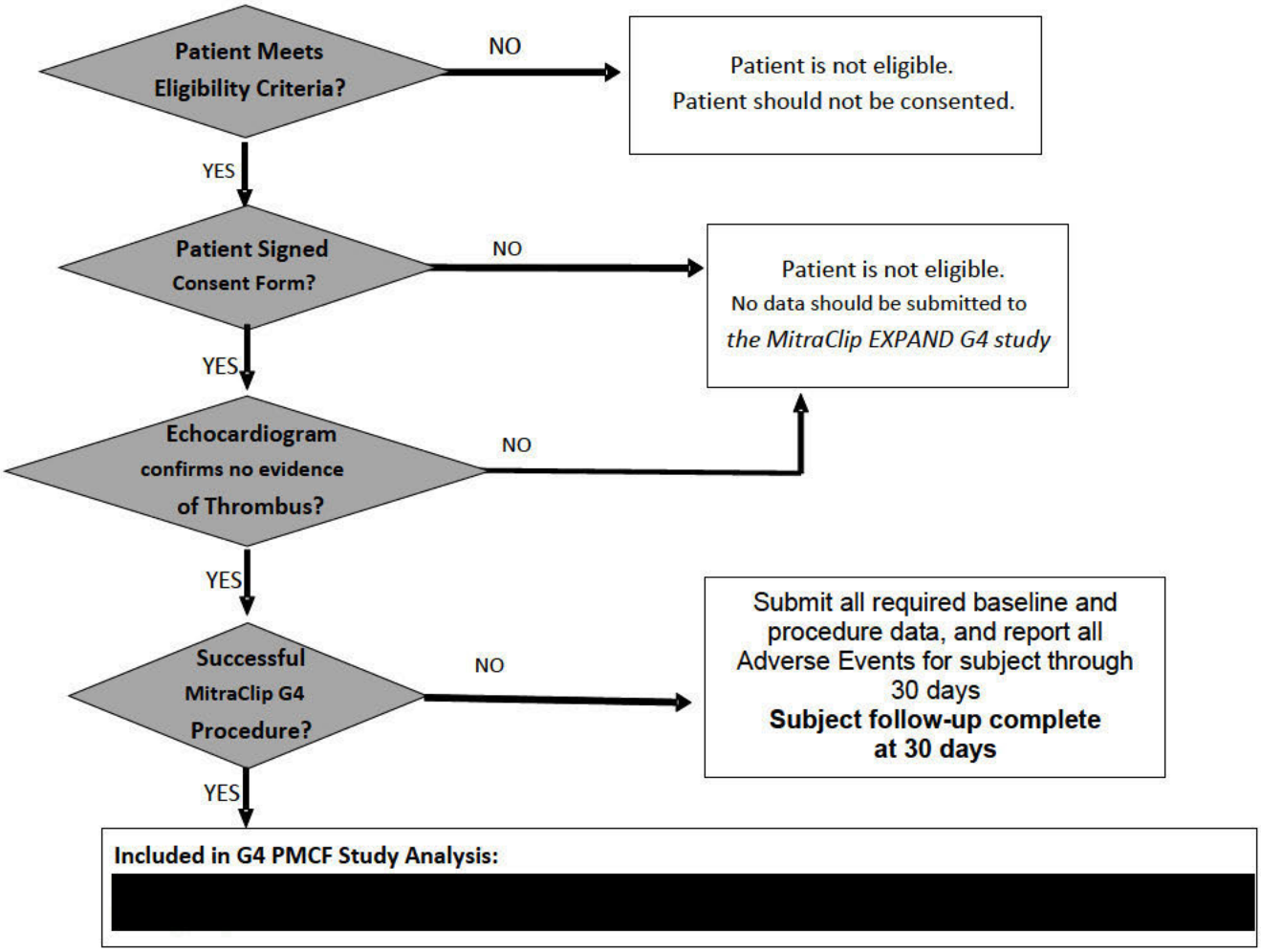

FIGURE 2: Schematic for Study Inclusion and Flow

3.2 Early Termination of the Clinical Study

No formal statistical rule for early termination of the MitraClip G4 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 Institutional Review Board/Ethics Committee (IRB/EC).

4.0 STUDY 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 All-cause Death, Myocardial Infarction, Stroke, or non-elective CV surgery for device related complications
- MR Severity (evaluated at discharge, 30 days, 1 year and 5 years)
- Device Related Adverse Events (including mitral valve stenosis, device embolization, single leaflet device attachment (SLDA), 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
- Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- New York Heart Association (NYHA) functional class improvement
- 6 minute walk distance (6MWD) (per standard of care)

4.3 Success Criteria:

The MitraClip G4 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 [redacted].

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 G4 System. The study will include a minimum of [redacted] 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 G4 PMCF Study if they are eligible per the inclusion/exclusion criteria.

[redacted]

5.2.2 Informed Consent

Patient Information and Consent Form must receive approval of Sponsor and Ethics Committee (EC) or Institutional Review Board (IRB) prior to beginning enrollment into the MitraClip G4 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 G4 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) EC/IRB approved informed consent prior to any data is reported into this 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/IRB, subjects from vulnerable populations may be enrolled in the study. The ISO14155 definition of vulnerable population is as follows: A 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 consented subjects treated commercially with the MitraClip G4 System will be considered. All subjects must meet the criteria below before being enrolled into the MitraClip G4 PMCF 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

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

Per ISO 14155, the patient is considered enrolled upon signing and dating an informed consent for participation.

5.5 Total Expected Duration of the Study

The time to complete the MitraClip G4 PMCF study is estimated to be approximately [redacted] years.

5.6 Expected Duration of Each Subject's Participation

The final required visit for subjects in the MitraClip EXPAND G4 Study is at [redacted] years post-procedure. Therefore, the expected duration of participation for subjects is approximately [redacted] months.

5.7 Number of Subjects Required to be Included in the Study

Approximately [redacted] subjects will be included in the MitraClip G4 PMCF Study.

5.8 Estimated Time Needed to Select this Number

The estimated time to enroll [redacted] patients is about [redacted] months.

5.9 Subject Discontinuation

Subjects that are consented and receive a MitraClip G4 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 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 FOLLOW UP ASSESSMENTS

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, 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. 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, MR severity, KCCQ Score and New York Heart Association (NYHA) Functional Class. If a 6-minute walk test is conducted as standard of care at baseline, these results will be collected in the G4 PMCF Study.

6.1.2 Pre-treatment Imaging

Pre-Treatment Transthoracic Echocardiogram (TTE) and Transesophageal Echocardiogram (TEE) should be conducted per standard of care for a MitraClip Procedure.

6.2 Index Procedure

All Investigators must read and understand the Instructions for Use (IFU) that accompanies the Device. Handling and preparation of the MitraClip G4 System should be in accordance with the IFU. The MitraClip procedure should be conducted in accordance with standard of care practice and approved labelling.

6.3 Post-procedure

Post treatment TTE, Clinical Assessments and Laboratory / Clinical Tests should be conducted prior to discharge per standard of care. Post-procedure information (the discharge time point) to be reported for this study include at minimum: Medical Exam and Reporting of Vitals, adverse events, MR severity, KCCQ Score and NYHA Functional Class.

6.4 Subject Follow-up

Follow-up is conducted per standard of care at 30 days and annually through 5 years 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.

[redacted]

[1]*Adverse Events to 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.

As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:
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.

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;
   5) Chronic disease.
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

A planned hospitalization for pre-existing condition, or a procedure required by the 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. DD information on the MitraClip accessories will also be collecting during G4 PMCF study.

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 clinical investigation 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 in section 7 per AE and SAE definitions. Adverse Events to be reported during this study include: all cardiovascular events, events classified as MAEs (as defined in section 4.2) and device-related complications (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 5 year follow up visit. 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 SAE Notification Form will be made available to allow the investigator to report required SAEs in the event the entry cannot be made in the Electronic Data Capture (EDC) System. 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 IRB/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 IRB/EC per the investigative site's local requirements. A device deficiency 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)

No CEC will be required for this study. Adverse events will be reported per site's assessment.

9.0 STATISTICAL ANALYSIS

9.1 Statistical Overview

This is a post-market multicenter study of consecutive consenting patients treated with the MitraClip G4 System at participating centers. The study will enroll a minimum of [redacted] subjects to collect clinical evidence for the MitraClip G4 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

[redacted]

9.3 Sample Size Calculations and Assumptions

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.4 Statistical Analyses

9.4.1 Study Endpoint Analyses

The primary endpoint of the MitraClip G4 PMCF study 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. This endpoint will be assessed as a proportion of subjects meeting the definition of APS, and tested against a performance goal (PG) of [redacted]

The null and alternative hypotheses are stated as:

H_0: APS rate ≤ PG
H_A: APS rate > PG

- True APS rate is assumed to be [redacted]
- PG is [redacted]
- One-sided type I error rate = 0.05

[redacted]

[redacted]

[redacted]

9.4.2 Clinical Endpoint Analysis

Descriptive analysis will be performed on clinical and safety endpoints defined in Section 4.0. 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 sex, 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 annualized event rate in event per patient-year.

9.4.3 Timing of Analysis

The analysis for the PMCF will be conducted when the last subject completes the 30 days visit.

9.4.4 Handling of Multiplicity Issues

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

[redacted]

9.4.5 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 Planned Interim Analysis

No formal interim analyses are planned for this study. Interim study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

9.6 Success Criteria

The primary endpoint for the PMCF study must be met for the study to be considered successful.

9.7 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 as required 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 the study of the MitraClip G4 System. 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 of the Protocol amendment (administrative changes) or obtaining EC's/IRB'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/IRB 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; 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 this 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/IRB 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 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) or Institutional Review Board (IRB) 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 IRB/EC, the Sponsor, and/or the regulatory agencies as needed.

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

14.0 RISK ANALYSIS

14.1 Anticipated Clinical Benefits

Treatment with the MitraClip has been shown to effectively reduce Mitral Regurgitation in several clinical studies (Table 1 of this protocol). Treatment with the MitraClip G4 System within this study is anticipated to offer this same established benefit. The changes to the MitraClip G4 System were designed to have the same clinical impact with added ease in grasping of the mitral leaflets during the implant procedure. Design validation study indicates that users also responded favorably to the simplified Clip deployment procedure, stating that it is significantly better to the MitraClip NTR/XTR deployment procedure. Users rated leaflet grasping and capture with MitraClip G4 as better than leaflet grasping and capture with MitraClip NTR/XTR. Data from this study may help to further identify benefits of the MitraClip G4 device in improving mitral leaflet grasping and improve clinical outcomes.

14.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Please refer to the approved Instruction for Use for possible adverse events of the MitraClip G4 procedure.

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 G4 device as part of this study is identical to treatment with the MitraClip G4 device outside of this study. Participation in the study will not impact the MitraClip G4 procedure or use of the MitraClip G4 System in any way, therefore there is no added procedural risk by participating in this study.

Participation in the study requires submission of data that may or may not be protected heath 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

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.

In the study, the device is required to be used in accordance with the MitraClip G4 System IFU. Contraindications, warnings and precautions will be provided with all devices to be used during this study per the IFU.

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 [redacted] patients in clinical trials or registries, and more than [redacted] 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 G4 implant within this study are identical to the risks of receiving a MitraClip G4 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 the enrollment of patients treated with the MitraClip G4 System into this study.

Clinical Investigation Plan

ANNEX 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 Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) Registry
IFU	Instructions for Use
IRB	Institutional Review Board
IVC	Inferior Vena Cava
MAE	Major Adverse Event
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

ANNEX 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 and section 7.1 of this protocol.

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[23]
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

[23] JACC, Vol 32, No.5,November 1, 1998:pg1541, Table 21

Clinical Investigation Plan

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 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, sler'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 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 ≥ Type 3 based on a modified Bleeding Academic Research Consortium (BARC)[24] definition:

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

Type 4: CV Surgery-related bleeding
- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

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

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

MAJOR VASCULAR COMPLICATION
Any major complication, relating to, or affecting, the circulatory system as a result of the MitraClip procedure, including new onset of any of the following:
- Hematoma at access site >6 cm.;
- Retroperitoneal hematoma;

[24] 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.

- 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 ≥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 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, 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. 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)[25]: Rating will be: none, mild, moderate, or severe.

[25] 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

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.

Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017 Apr;30(4):303-371.

Clinical Investigation Plan

ANNEX 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.

Clinical Investigation Plan

ANNEX IV - SUMMARY OF CHANGES

[redacted]

Details of Change

The sample size calculation is revised to incorporate contemporary clinical evidence in evaluation of the primary endpoint. Please see Section 9.3 for details.

Follow up duration is revised to 5 years (product lifetime) as described in 6.4.

END OF MitraClip G4 PMCF Study Protocol

[redacted]

Clinical Investigation Plan

APPENDIX III - ABBREVIATIONS AND ACRONYMS

A2-P2	Second location on anterior and posterior leaflets
AE	Adverse Event
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ASD	Atrial Septal Defect
CI	Confidence Interval
CRF	Case Report Form
CV	Cardiovascular
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DD	Device Deficiency
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EDC	Electronic Data Capture
EU	European Union
GRASP	The GRASP Registry
IFU	Instructions for Use
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IVC	Inferior Vena Cava
MAE	Major Adverse Event
MitraClip XTR	MitraClip XTR System
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Clinical Investigation Plan

APPENDIX IV - DEFINITIONS

ANTICIPATED ADVERSE EVENT
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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[26]
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

[26] JACC, Vol 32, No.5,November 1, 1998:pg1541, Table 21

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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 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, sler'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:

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.

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MAJOR ADVERSE EVENT (MAE)

MAE is a 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 ≥ Type 3 based on a modified Bleeding Academic Research Consortium (BARC)[27] definition:

Type 3

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

Type 4: CV Surgery-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

Type 5: Fatal bleeding

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

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

MAJOR VASCULAR COMPLICATION

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

- Hematoma at access site >6 cm.;
- Retroperitoneal hematoma;

[27] 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.

- 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 ≥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 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. 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)[28]: Rating will be: none, mild, moderate, or severe.

[28] 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.

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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.

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APPENDIX V - Case Report Forms

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

Appendix VI- LITERATURE REVIEW AND SUMMARY OF post-market TRIALS

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 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.[29] 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-EU[30] 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

[29] 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.

[30] 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.

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 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 registry[31]. 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

[31] Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistritto 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.

Attizzani et al.[32] 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 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 ≤25%, 28 patients had LV end systolic diameter >55 mm, 34 patients had coaptation depth ≥11 mm, and 10 patients had the flail width ≥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 ≥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 ≤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 ≥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.

[32] 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.

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Several reports on TRAMI have been published over the years[33,34]. The largest prospective cohort was described by Puls et al.[35]. 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.

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 of patients (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.

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[33] 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.

[34] 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.

[35] 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.

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±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 ≤2+ was achieved in 98.2% of patients post-procedure with no difference between MR etiologies. At 1-year, MR was reduced to ≤2+ in 94.0% of patients and 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-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-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 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)[36] 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±8.1%.

[36] 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.

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

In a separate analysis, Tay et al.[37] 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.

[37] 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.

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.[38] 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 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 cm^2 (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 ≤2+ was achieved in 93.0% of patients, while MR grade ≤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 ≤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 ≤2+ was similar at sites with and without precommercial experience (93.8% vs. 91.1%, p=0.26), though reduction to MR grade ≤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.

[38] 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.

1-Year Outcomes (Nov 2013 – Sep 2015)

In a subsequent report, Sorajja et al.[39] 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.

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 cm^2 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 ≤2+ was achieved in 93.0% of patients, while MR grade ≤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 co-morbidities 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.

[39] 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.

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 ≤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 ≤1+ (21.7% and 35.7%, respectively) compared to those discharged with MR 2+ (29.2% and 39.2%, respectively), and MR ≥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

Clinical Investigation Plan

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.[40] 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.

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 ≥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 ≥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

[40] 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.

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 ≥10mm. 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.

Clinical Investigation Plan

APPENDIX VII: MONITORING PLAN

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

Clinical Investigation Plan

APPENDIX VII: CONTACT INFORMATION

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

Clinical Investigation Plan

APPENDIX IX: FORESEEABLE ADVERSE EVENTS

Please see device instructions for use regarding potential adverse events.

Clinical Investigation Plan

APPENDIX X - Summary of Changes

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