Abbott

Clinical Investigation Plan (CIP)

Prospective One-Center Clinical Approbation Assessment of The Symptomatic Chronic Severe Mitral Regurgitation Treatment with MitraClip NT System

Redacted Version B
Nov 15, 2021

2019

Protocol Name and Version Number	**ABT-CIP 10334 Version 1.0**
Date	13 December 2019
Coordinating Clinical Investigator/Study Principal Investigator:	[redacted] *(Chief Researcher, Doctor of Medical Sciences, Head of the Laboratory of Hybrid Methods of the Treatment of Cardiovascular Diseases)*
Study Co-Principal Investigator	[redacted]
Planned Number of Sites and Region(s)	**1 Site:** Federal State Budgetary Institution "National Medical Research Center of Cardiology" of the Ministry of Health of the Russian Federation (*short name - FSBI "NICC of Cardiology" of the Ministry of Health of Russia*). Address: 121552, Moscow, st. 3rd Cherepkovskaya, d.15A.
Clinical Investigation Type	A prospective, single-center study
Sponsor	Limited Liability Company ABBOTT LABORATORIES (LLC "ABBOTT LABORATORIES") 125171, Russia, Moscow, Leningrad highway 16A, building 1 Tel.: +7 (495) 258 42 80/81
CIP Author of Current Version	[redacted]

[redacted]

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: [redacted]

Signature:

Date:

[redacted]

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155:2011 standards and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

1.0 INTRODUCTION

1. Analysis and evaluation of clinical data of documents and materials submitted by the Applicant

The purpose of this study is to evaluate the MitraClip NT Systemfor safety and efficacy of use in the Russian population. The following properties and characteristics of the MitraClip NT System have already been studied and evaluated in earlier studies:

a) intention for use;
b) description of the medical devices including all components and variants (detailed specification of the device);
c) type testing of medical device (technical, toxicological tests);
d) conditions by which medical device is used (humidity, temperature, atmosphere pressure);
e) determination of indications and contraindications to the use of a medical device
f) determination of technical parameters, characteristics of the medical device;
g) the recommended method of use of medical device;
h) safety requirements and precautions;
i) disinfection, pre-sterilization cleaning and sterilization (if applicable);
j) the predicted result of treatment (efficacy and safety) and the expected side effects / adverse events.

2. Collection of clinical data

The scientific publications and other clinical data related to the use of the MitraClip NT System manufactured by Abbott Vascular, USA collected in other studies is available and is being submitted as part of the submission. The data are provided in hard copies or electronic (links in the internet). Also, additional analysis of analogue medical devices is provided as applicable.

3. Analysis and evaluation of clinical data, documents and materials

The following documents are provided by the applicant for evaluation:

a) information about analogues of medical device. Determination of the difference between MitraClip NT System device and its analogues;
b) risk analysis;
c) determination of the safety and efficacy of the MitraClip NT System;
d) the advantages by use if medical device and its analogues according to literature data;
d) determination of the reliability of medical device;
e) analysis of possible complications and side effects and methods for their elimination;
d) stability tests, shelf life reports.

Additionally, an analysis of diseases (pathological conditions) for which we use the MitraClip NT System is being provided. An evaluation of the effectiveness, safety and feasibility of the procedures (manipulations) using the MitraClip NT System are conducted. In addition, before conducting a clinical trial in accordance with GOST EN ISO 14971 “Medical devices. Application of risk management to medical devices”, the levels of risks associated with the test product should be determined. A detailed risk analysis will include or reference an objective analysis of published and available unpublished medical and scientific data. To take a decision about the starting a clinical trial in humans, it is necessary that the residual risks identified during

the risk analysis, as well as the risks for the patient associated with the clinical procedures are outweighed by the health benefits to the patient. This risk analysis should also be used as the basis for determining the expected adverse effects of the product, characterized by their nature, field of application, severity and consequences. Analysis and evaluation of the available clinical data provided here allow us to determine and justify the design of the planned study with the participation of patients, criteria for selecting patients, the main target indicators for evaluating the success of treatment, and the duration of the observation, to make judgments about the effectiveness and safety of using the MitraClip NT System, manufactured by Abbott Vascular (Abbott Vascular), USA, and principles of its work.

4. Evaluation of information about clinically significant corrective actions taken, including the suspension of the use of the MitraClip NT System, recall actions

The collection and analysis of the data regarding clinically significant corrective actions is compiled from open sources of Roszdravnadzor, other possible Internet resources, as well as based on the information provided by the manufacturer, and is included in the submission for evaluation.

5. Visual evaluation of medical device

A visual evaluation of the product will be carried out on the samples provided for the study. Data will be captured on following parameters of the MitraClip NT System: ergonomics, aesthetics, ease of use, operability and compatibility of components.

6. Clinical trials on human

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Background and Rationale

Mitral valve disease (MD) is the most common form of heart disease. The frequency of new cases of MD malformations significantly increases with age, from less than 2% at the age of up to 65 years, to 8.5% for the age group 65–75 years and 13.2% in the age group 75 years and older. Mitral regurgitation (MR) is one of the types of malformation of the MD, which involves lack of coaptation of the valve leaflets, which leads to a reverse flow of blood from the left ventricle to the left atrium. A pronounced progression of MR has a poor prognosis and leads to left ventricular failure, pulmonary hypertension, atrial fibrillation, stroke and death. Depending on the etiology, MR is classified into 2 types: (1) primary, or degenerative, and (2) secondary, or functional.

Degenerative MR (DMR) is caused by anatomical changes in the leaflets and chords of the mitral valve and is the most common type of MR in the world. Functional FMR (FMR) is caused by remodeling and dyssynchrony of the left ventricle and is usually associated with cardiomyopathy, or coronary heart disease; MR is secondary to left ventricular dysfunction, the mitral valve itself is morphologically normal. According to the treatment guidelines, surgical reconstruction is the preferred treatment option for chronic degenerative MR (DMR). Other treatment options include surgical valve replacement surgery. Despite the stringent requirements imposed during the operation, these methods are characterized by high mortality during the

operation, reduced survival, worse retention of postoperative left ventricular function and higher long-term morbidity.

Functional MR includes ischemic MR (fixation of the posterior cusp, leading to a posteriorly directed release of MR inside the left atrium) and non-ischemic MR (displacement of both papillary muscles, resulting in a center-directed release of MR). The prevalence of FMR is underestimated due to its "secondary" nature (patients present with heart failure CH is more likely due to LV dysfunction than heart disease). With this type of MR, pharmacotherapy is the preferred first-line therapy. Other treatment options include surgical reconstruction or surgical valve replacement. Surgical interventions of this type remain problematic, partly due to the fact that patients are characterized by severe comorbidities. Moreover, these patients have a high probability of postoperative relapses from moderate to severe MR, and there is no evidence that operations of this kind prolong life.

To minimize the risks associated with surgery, or to treat inoperable patients, a new class of therapy was developed based on transcatheter methods, the so-called "edge-to-edge" casement reconstruction. Percutaneous combination procedure can be considered for both patients with symptomatic severe primary MR, and secondary MR. This type of therapy is considered for patients who are considered inoperable or at high risk for open-heart surgery and have a life expectancy of more than 1 year. This procedure is unique and can be performed using the **MitraClip NT** implantable clip.

At the moment, more than 40,000 procedures have been performed worldwide using **MitraClip NT System**. The system is a transcutaneous implantable mechanical clamp that is used to increase the coaptation of the mitral valve leaflets, resulting in significant reduction of mitral regurgitation through the heart cycle. According to studies published in, patients show a greater safety profile after 12 months compared with the research group that underwent the traditional operation.

As a result, the purpose of this study will be the clinical evaluation of the effectiveness of the **MitraClip** NT System in the treatment of symptomatic chronic severe mitral regurgitation.

1.2 Rationale for Conducting this Clinical Investigation

Mitral regurgitation is the most common pathology of the heart valve in the world. Patients with severe MR experience various symptoms of exhaustion, such as shortness of breath, an abnormal heart rhythm, dizziness, and fatigue. The quality of life of such patients suffers greatly, their mobility is limited, the number of hospitalizations associated with heart failure increases, and mortality increases. Chronic severe MR is often associated with heart failure; in addition, it can be fatal if left unattended.

Although surgery to restore or replace the mitral valve is currently considered a standard procedure for this case, many patients with clinically significant MR are at an unacceptable risk, and therefore no surgery is performed for them. To optimize the load, such patients are often forced to take various drugs (in particular, beta-blockers, ACE inhibitors, angiotensin II receptor blockers), which can temporarily relieve MR symptoms, but do not eliminate their cause. As a result, a significant proportion of patients receiving medical treatment

continue to develop heart failure and deteriorate the quality of life. In this regard, there is a significant clinical need to search for treatment options for moderate to severe MRI for patients with a high level of surgical risk.

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

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Overview

The objective of this study is to evaluate safety and effectiveness of the MitraClip NT procedure in the Russian population for treatment of Mitral Regurgitation.

2.2 Devices To Be Used in the Clinical Investigation

2.2.1 Name of the Devices Under Investigation

The table below provides the list of the medical devices imported into the Russian Federation for the purpose of this clinical investigation.

Table 1 – Numbers of Devices Under Investigation

Device name	Model/Type	Serial/Lot Controlled	Manufacturing Date/Expiration Date	Quantity	Investigational or Market Released
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2.2.2 Indication for Use

MitraClip NT Clip is intended for reconstruction of the insufficient mitral valve through tissue approximation.

2.2.3 Description of the Devices Under Investigation

MitraClip NT System consists of 2 parts:
1) Delivery Catheter (hereinafter «*MitraClip NT Delivery Catheter /Delivery catheter*»);
2) Steerable Guide Catheter with dilator.

MitraClip NT Clip Delivery System

The Clip Delivery System (Figures 1, 3 and 4) is used to advance and manipulate the implantable MitraClip NT Device for proper positioning and placement on the mitral valve leaflets. The Clip Delivery System is designed to deploy the implant in a way that requires multiple steps to ensure safe delivery of the device.
In Fig. 1 shows a general view of the device.

The Steerable Sleeve is used to position and orient the **MitraClip NT** Clip Delivery System in the appropriate location above the mitral valve. Steerable Guide Catheter is also used to properly position **MitraClipNT** System on the mitral valve. A dilator is used to introduce a catheter into the femoral vein and the left atrium.

The Clip Delivery System consists of three major components: 1) the Delivery Catheter 2) the Steerable Sleeve and 3) the MitraClip NT Device. The Clip Delivery System is introduced into the body through a Steerable Guide Catheter which includes a dilator.

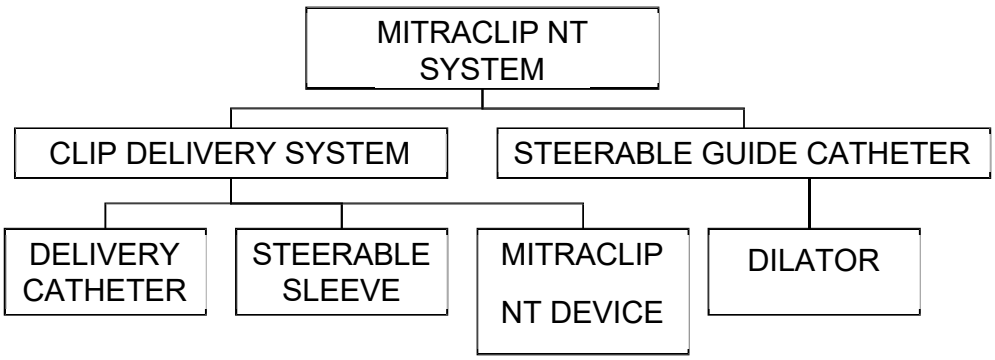

Figure 2 – Main Parts

The Delivery Catheter and Steerable Sleeve handles (Figure 3) provide the user with the means to position, actuate, and deploy the **MitraClip NT** Device. The Delivery Catheter handle consists of a Fastener, Lock Lever, Actuator Knob, Arm Positioner, Gripper Lever, and two flush ports. The Fastener is used to temporarily secure the Delivery Catheter position relative to the Steerable Sleeve, to prevent inadvertent manipulation of the **MitraClip NT** Device once the leaflets have been grasped. The Lock Lever is used to lock and unlock the lock mechanism of the **MitraClip NT** Device. The Arm Positioner is used to open, close, and invert the **MitraClip NT** Device Arms and advance or retract the actuator mandrel. The Gripper Lever is used to hold the Grippers in the raised position or to release them to the lowered position. The Actuator Knob is rotated in the counterclockwise direction to unthread the actuator mandrel from the **MitraClip NT** Device threaded stud. The flush ports are standard female luer fittings that allow for aspiration of air and infusion of liquids (e.g., heparanized saline) into the thru-lumens of the Delivery Catheter.

The Delivery Catheter consists of a long, flexible hydrophilic-coated multi-lumen shaft secured to the **MitraClip NT** Device at the distal end and to a handle at its proximal end. The lumens are used as conduits for the **MitraClip NT** Device release lines (i.e., Lock Lines and Gripper Lines) and the **MitraClip NT** Actuator Mandrel. The distal tip of the Delivery Catheter is radiopaque to allow visualization under fluoroscopy and is designed to be securely attached to the **MitraClip NT** Device. The Steerable Sleeve is used to position and orient the **MitraClip NT** Clip Delivery System and **MitraClip NT** Device in the appropriate location above the mitral valve.

[redacted]

MitraClip NT Device (Clip)

The **MitraClip NT** Device (Figure 4) is a single sized, percutaneously implanted mechanical Clip. The **MitraClip NT** Device grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The **MitraClip NT** Device is placed without the need for arresting the heart or cardiopulmonary bypass. The implantable **MitraClip NT** Device is manufactured from nitinol (Gripper and Leaf spring); polyester fabric (Gripper and Clip covers), cobalt-chromium alloy and polypropylene tubing that are commonly used in cardiovascular implants.

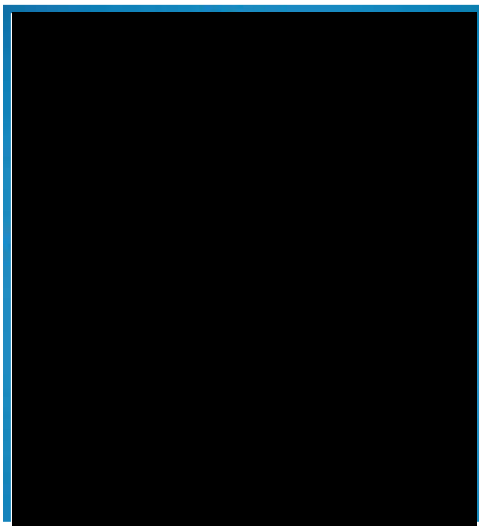

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Figure 4 - MitraClip NT Device

The **MitraClip NT** Device arms can be adjusted to any position from fully opened, fully inverted, and fully closed, as shown in Figure 5. These positions are designed to allow the **MitraClip NT** Device to grasp and approximate the leaflets of the mitral valve using controls on the Delivery Catheter Handle. The **MitraClip NT** Device can be locked, unlocked, and repeatedly opened and closed. The Grippers can be raised or lowered repeatedly.

The Steerable Guide Catheter

The Steerable Guide Catheter consists of a hydrophilic-coated multi-lumen shaft, a radiopaque distal tip ring, an atraumatic distal soft tip, and hemostasis valve located at the distal end of the handle. The Steerable Guide Catheter is steered and actuated by the use of a control knob located on the handle. Four lumens spaced within the catheter shaft wall provide conduits for cables which transmit tension to the distal tip when the control knob (+/-) is turned on the handle. The Steerable Guide Catheter and Dilator are designated for professional use only.

The hemostasis valve is designed to accommodate the dilator and subsequent use of the **MitraClip NT** Clip Delivery System (CDS). The hemostasis valve minimizes or prevents blood backflow through the catheter thru-lumen as well as minimizes the risk of air introduction into the vasculature. An alignment marker is placed on the hemostasis valve to aid in the proper insertion of the CDS into the Guide. The flush port is a standard female luer fitting that allows for aspiration of air and infusion of liquids into the thru-lumen of the Guide.
The Dilator consists of a single lumen extrusion secured to a standard rotating hemostasis valve. The dilator has an echogenic tapered distal tip with a molded spiral groove. The Dilator is used for the introduction of the Guide into the femoral vein and left atrium.

Figure 6 - Steerable Guide Catheter and Dilator

Silicone Plate is used in a sterile field. It is placed on the lift under the stabilizer to prevent accidental displacement of the stabilizing device during the procedure. Fasteners are used in a sterile field to fix the steerable guide catheter and **MitraClip NT Device**to the stabilizer.

Silicone plate and fasteners are designed for single use and are provided sterile, complete with a steerable guide catheter.

Accessories

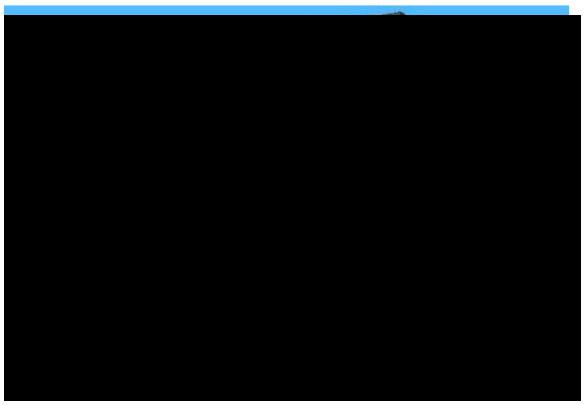
With **MitraClip NT System**, accessories are used, including: 1) a stabilizer, 2) a lift, 3) support plate. The stabilizer device is a non-sterile, reusable device that must be cleaned and sterilized before each use.

The lift and the support plate are used outside the sterile field as a stable platform for the stabilizer on which the **MitraClip NT System** and steerable guide catheter are located. Follow the instructions for cleaning and storing devices.

The stabilizer is used in a sterile field as a support and positioning device for the steerable guide catheter and **MitraClip NT** Clip Delivery System. It is not intended for repeated use, it must be sterilized before each use.

Support Plate

Support Plate (Figure 7), is placed under the patient's foot to stabilize the remaining parts, before covering the sheets for the procedure.

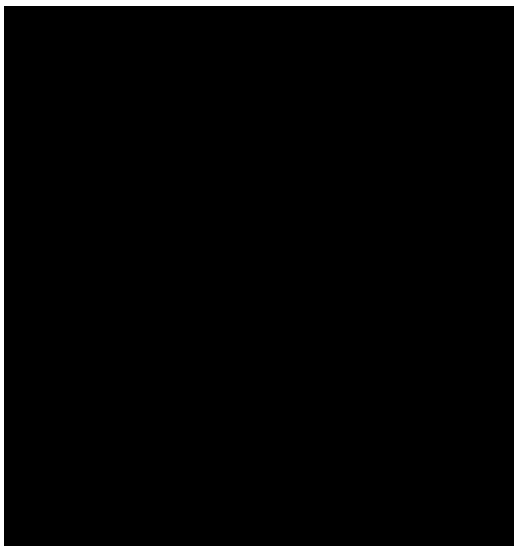


Lift

Lift (Figure 9), is installed on the support plate above the patient's foot.

Stabilizer

For the procedure, the patient is covered with a sterile sheet, and a sterile stabilizer, (Figure 9), is placed on top of the sheet, directly on the sterile silicone plate that is on the lift. The **MitraClip NT** and steerable guide catheter are fixed to the stabilizer with sterile fasteners.



Please refer to the IFU for additional information regarding the device used in this clinical investigation.

2.2.4 Summary of Previous Clinical Studies

This section summarizes results of relevant studies of the MitraClip NT System Clinical Program. Please refer to the Investigator Brochure for a summary of the clinical investigations sponsored by Abbott and all published data on the MitraClip therapy in addition to the relevant previous clinical experience with medical devices that have similar characteristics, and the history of adverse device effects.

Rationale for the MitraClip NT System Russian Trial is subsequently presented in the context of this scientific body of evidence.

EVEREST I Design and Results

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

A total of 55 patients were enrolled in the trial. The **MitraClip** device was implanted in 89% of patients and the trial met its pre-specified safety acceptance criterion, demonstrating mechanistic feasibility of implant and safety of the **MitraClip** System and procedure. There were no intra-procedural deaths. The procedure time averaged approximately 4 hours, patients were hemodynamically stable during the procedure, and the average length of hospital stay was approximately 3 days. A majority of patients (70.9%) experienced reduction in MR severity to 2+ or less at discharge. No **MitraClip** device embolizations occurred in this cohort. The rate of single leaflet device attachment (SLDA) in this initial cohort of patients treated was 10.2%. A majority of SLDAs were detected early (within 30 days post- **MitraClip** procedure). Patients demonstrated

improvement in NYHA Functional Class and left ventricular measurements that were sustained through 5 years. At 5 years, freedom from death was 86.4% and freedom from mitral valve surgery was 55.1%. The results of the EVEREST I trial at 5 years provide evidence of the safety and long-term durability of the **MitraClip** device in the early cohort of patients treated in the United States.

EVEREST II Randomized Controlled Trial (RCT) Design and Results

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

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

Patients who underwent the **MitraClip** procedure experienced a 30-day major adverse event rate (composite of death, myocardial infarction (MI), re-operation for failed surgical repair or replacement, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, ventilation for greater than 48 hours, GI complication requiring surgery, new onset of permanent atrial fibrillation, septicemia and major bleeding complication) of 7.9% versus 50% in patients who underwent mitral valve surgery in the Control group. Excluding the most common event of major bleeding complication, **MitraClip** device patients still experienced a lower major adverse event rate (4.5%) than surgery patients (11.3%) (p=0.057).
Through 30 days, **MitraClip** patients experienced a lower site-reported adverse event rate than surgery patients in the following categories: cardiac rhythm disorders (atrial arrhythmias, bradyarrhythmia, ventricular arrhythmia), congestive heart failure, peripheral edema, anemia, infections, neurologic events and respiratory events. At 30 days, **MitraClip** patients experienced a higher event rate than surgery patients in the following categories: atrial septal defect, myocardial ischemia, residual or recurrent MR, single leaflet device attachment (SLDA), gastrointestinal bleed, and vascular complications such as hematoma, bleed or bruising. Beyond 30 days through 5 years, site-reported adverse events occurred at a low rate in both **MitraClip** and surgery patients and there was no signal for an elevated adverse event rate in either group.

[redacted]

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

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

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

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

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

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

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

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

The EVEREST II High Risk Registry is a single-arm prospective, multi-center clinical trial enrolling high surgical risk patients with moderate-to-severe (3+) or severe (4+) MR. Patients were considered high surgical

risk if either their Society of Thoracic Surgery (STS) predicted operative mortality risk was ≥ 12%, or the surgeon investigator determined the patient to be high risk due to the presence of pre-specified risk factors. After undergoing the **MitraClip** procedure, patients were followed at discharge, 30 days, 6, 12, 18 and 24 months and yearly thereafter through 5 years. All patients have completed the required 5 years of follow-up and the study is now closed. An independent Echocardiograpy Core Laboratory (ECL) assessed MR severity and other echocardiographic parameters at baseline and follow-up.

A total of 78 patients were enrolled in the EVEREST II High Risk Registry. The device was implanted in 96.2% of patients. There were no intra-procedural deaths. The procedure time averaged approximately 3 hours, patients were hemodynamically stable during the procedure, and the average length of hospital stay was less than 4 days. A majority (75.6%) of these high surgical risk patients were discharged home without home healthcare. A majority of patients (71.8%) experienced reduction in MR severity to 2+ or less at discharge post- **MitraClip** procedure.

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

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

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

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

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

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

Eligibility for the Non-High Risk arm was the same as for the EVEREST II RCT and that for the High Risk arm was the same as for the HRR.

Enrollment in the Continued Access REALISM study was initiated on January 22, 2009. A total of 899 patients (628 High Risk, 271 Non-High Risk) were enrolled and treated in the EVEREST II REALISM Continued Access Study. Enrollment in the Non-High Risk arm of the study concluded on April 14, 2011 and enrollment in the High Risk arm concluded on December 19, 2013.

In the United States, patients that did not meet the eligibility criteria for REALISM were treated under FDA's special IDE for Compassionate Use and Emergency Use. A total of 59 Compassionate Use patients and 7 Emergency Use patients have been treated under these IDE provisions between December 14, 2010 and February 22, 2013.

As expected, the high risk patients had a higher incidence of significant co-morbidities than the non-high risk patients. Patients enrolled in the REALISM High Risk arm had similar baseline characteristics and co-morbidities as those enrolled in the High Risk Registry. Although patients enrolled in the REALISM Non-High Risk arm under the same eligibility criteria as the EVEREST II RCT, REALISM Non-High Risk patients were older on average by 7 years than the EVEREST II RCT patients.

Mortality and major adverse events at 30 days and 12 months in the REALISM High Risk and Non-High Risk arms were consistent with the arm (high risk vs non-high risk) in which they were enrolled. Safety results of the REALISM study provide further evidence that the "real-world" use of the **MitraClip** device continues to perform as expected based on the EVEREST II Randomized Controlled Trial and High Risk Registry.

<u>COAPT Randomized Controlled Trial (RCT) Design and Results</u>
The COAPT Trial is a prospective, randomized, parallel-controlled, multicenter clinical evaluation of the MitraClip Device for the treatment of clinically significant FMR in symptomatic HF subjects who are treated per SoC and who have been determined by the site's local heart team as not appropriate for MV surgery. COAPT enrollment was limited to a maximum of 100 investigational sites. During the enrollment phase, 614 subjects were randomized at 78 investigational sites. An additional 51 roll-in subjects were treated by operators at 34 sites without recent or prior experience with the MitraClip Device, in order to gain hands-on experience before randomizing subjects in the trial. Patients were randomized in a 1:1 ratio to the MitraClip Device or to Control group (no device). Randomization was stratified by study site and cardiomyopathy etiology (i.e. ischemic or non-ischemic).

Subjects were elderly, with a mean age of 74.5-years in roll-In subjects and 72.2-years in randomized subjects. Females comprised 37.3% of roll-In subjects and 36.0 % of randomized subjects. Baseline NHYA Functional Class was predominantly II/III. Mean LVEF was 36.7% in the roll-In cohort and 31.3% in the randomized cohort. The STS mortality risk scores reflect a population of highly comorbid subjects with a mean replacement score of 11.1% and 8.2% for roll-in and randomized subjects, respectively, and a mean repair score of 7.9% and 5.8% for roll-in and randomized subjects, respectively. Majority of subjects in both

the roll-In and randomized cohorts presented with prior MI, CAD, hypertension, hypercholesterolemia, arrhythmia, and renal disease.
Diabetes and history of percutaneous transluminal coronary angioplasty (PTCA) were present in over one third of subjects, with COPD additionally present in over one-third of roll-In subjects. Approximately half of the subjects in the roll-In cohort and 40% in the randomized cohort had prior coronary artery bypass grafting (CABG) surgery.
Follow-up visits were required at 1 week (phone contact), 30-days, 6-months, 12-months, 18 months, 24-months, and annually thereafter through 5-years.

The COAPT 3-year data was recently presented at the 2019 Transcatheter (TCT) conference at San Francisco by Dr. Michael Mack with the August 2, 2019 data cut-off date. Consistent with the 2-year outcomes, the patients in the device (MitraClip + GDMT) arm continued to see significant benefit over the control (GDMT only) arm in the COAPT study. Overall 58 out of 312 GDMT patients (18.6%) had crossed over to the MitraClip arm at this timepoint (crossover was allowed after 2 years of follow up per protocol). Primary effectiveness of all hospitalizations for HF were 169 in 95 patients in device arm vs 299 in 158 patients in control arm at 2 years (NNT=3.1 [95% CI 1.9, 8.2]. Same trend was observed with 220 HFH in 114 patients in device arm vs 378 in 196 patients in control arm at 3 years (NNT=3.0 [95% CI 2.4, 4.0] per the ITT analysis. The benefit to the patients in the device arm was even more pronounced if the control patients who crossed over to the device arm were censored at the time of crossover (NNT=2.8 [95% CI 2.2, 3.7] at 3 years. All-cause mortality or HF hospitalization had similar trend with event rate of 58.8% for device arm and 88.1% for control arm at 3 years (NNT = 3.4 [95% CI 2.7, 4.6], again more pronounced with censoring of the control patients at the time of crossover (NNT=3.5 [95% CI 2.8, 4.8] at 3 years.
The freedom from device related complications (primary safety endpoint) did not show any worsening in the 2-3 year period and was identical to the 2 year outcomes of 1.4% for the true device related complications (SLDA, device embolization, endocarditis/mitral stenosis requiring surgery, or any other device related complication requiring surgery). The progressive heart failure requiring LVAD or heart transplant however increased from 3.8% to 7.4% from 2-3-year period owing to the very aged population with multiple comorbidities.
The quality of life as assessed by ANCOVA analysis of the KCCQ summary score for complete 2-year data showed an improvement of 7.8±2.3 points for the device arm compared to decline of 12.1±2.3 points for the control arm. Similarly, 6MWD outcomes showed a decline of 55±10.8 points for the device arm vs decline of 93.5 ±10.9 for the control arm. Adverse event rates were consistently low and strongly in favor of the device arm. Overall, the data concluded that at 36 months transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, QOL and functional capacity compared to GDMT alone.

Based on this clinical evidence clinical benefit of MitraClip System continues to demonstrate significant benefit to MR patients and is suitable for use in the study for safety and efficacy in the Russian population.

2.2.5 Description of the Control Devices

N/A.

2.2.6 Device Handling

The Sponsor requires the clinical site to store all investigational products according to the labeling and Instructions for Use in a secure area to prevent unauthorized access or use.

3.0 CLINICAL INVESTIGATION DESIGN

3.1 Clinical Investigation Procedures and Follow-up Schedule

The Flow Chart and the Follow-up requirements of this clinical investigation are described below.

Figure 10: Clinical Investigation Flow Chart

Overall Flow of the Trial and Follow-up Schedule

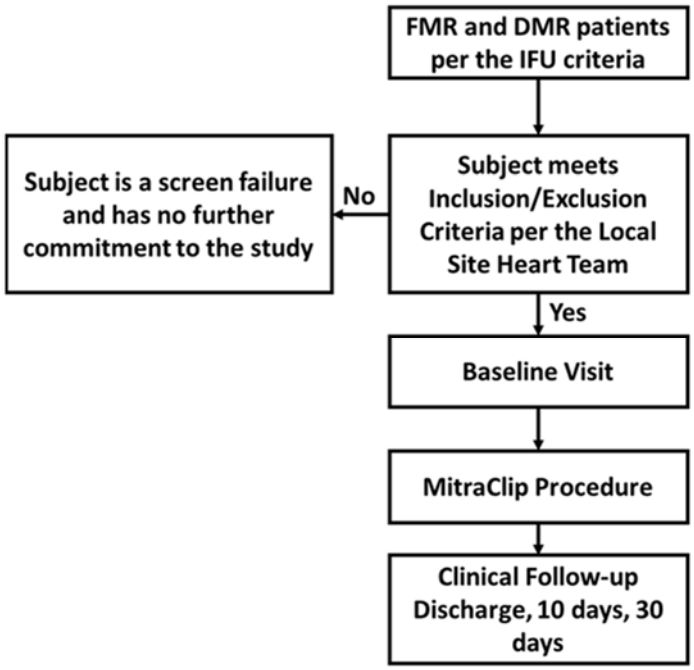


Figure 10 – Flow-chart

3.2 Early Termination or Suspension of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation 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 (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- An oversight committee (e.g., Steering/Executive Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled.

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials (including devices) to the Sponsor, and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP.

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

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

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

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

4.0 ENDPOINTS

4.1 Primary Endpoint

Successful implantation of the MitraClip NT device resulting in a decrease in the MR severity grade as assessed from the discharge echocardiogram (10-day echocardiogram will be used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge will be considered a failure for the procedure.

4.2 Descriptive Endpoints

Clinical Endpoints:

- Technical Success: Alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a Clip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure
- Device Success at 30-day post-procedure: Alive with original intended Clip(s) in place, and no additional surgical or interventional procedures related to access or device since completion of the original procedure, and intended performance of the Clip(s) with MR reduction to ≤ mild and freedom from device related Serious Adverse Events (SAE)s (i.e. embolization, mitral stenosis, single leaflet device attachment, Iatrogenic atrial septal defect, myocardial perforation, or the need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip NT device)
- Procedural Success at 30-day post-procedure: No procedure related SAEs (i.e. death, stroke, MI, renal failure, and non-elective cardiovascular surgery for device or procedure related adverse events occurring after the attempted MitraClip procedure (i.e. femoral vein puncture for trans-septal access)
- All-cause mortality
- Number of hospitalizations and reason for hospitalization (i.e. heart failure, cardiovascular, non-cardiovascular) through follow up
- Major bleeding requiring transfusion through follow up
- Six Minute Walk Test (6MWT) distance at baseline, 10 days and 30 days
- Average doses of concomitant cardiac medications at baseline, procedure, 10 days and 30 days
- NYHA will be done on screening day, 10 days, 30 days

Device and Procedure-Related Endpoints:

- Implant Rate: Defined as the rate of successful delivery and deployment of one or more MitraClip NT devices with echocardiographic evidence of leaflet approximation and retrieval of the delivery catheter
- Device Procedure Time: Defined as the time elapsed from the puncture of the groin for the trans-septal procedure to the time the Steerable Guide Catheter is removed
- Total Procedure Time: Defined as the time elapsed from the first of intravascular catheter placement, or transesophageal echocardiogram (TEE), to the removal of the last catheter and TEE
- Device Time: Defined as the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip NT (CDS) is retracted into the Steerable Guide Catheter
- Fluoroscopy duration: Defined as the duration of exposure to fluoroscopy during the MitraClip NT procedure
- Length of stay in Intensive Care Unit/Critical Care Unit/Post-Anesthesia Care Unit (ICU/CCU/PACU)
- Length of hospital stay excluding rehabilitation stay
- Length of rehabilitation stay
- Location to which subject was discharged (home or another facility)
- If subject discharged to another facility, length of stay at facility to which subject was discharged
- Mitral valve surgery (including type of surgery), including reason for intervention

- Additional MitraClip NT device intervention, including reason for intervention

Echocardiographic Endpoints:

The following echocardiographic endpoints will be reported at baseline, discharge, 10 days, 30 days. Echocardiographic endpoints will be assessed at baseline, discharge, 10 days, 30 days.

- MR Severity Grade
- Effective Regurgitant Orifice Area
- Regurgitant Volume (RV)
- Regurgitant Fraction (RF)
- Left Ventricular End Diastolic Volume (LVEDV)
- Left Ventricular End Systolic Volume (LVESV)
- Left Ventricular End Diastolic Dimension (LVEDD)
- Left Ventricular End Systolic Dimension (LVESD)
- Left Ventricular Ejection Fraction (LVEF)
- Right Ventricular Systolic Pressure (RVSP)
- Mitral Valve Area (MVA)
- Mean Mitral Valve Pressure Gradient (MVG)
- Systolic Anterior Motion of the mitral valve (present or absent)
- Forward Stroke Volume (FSV)
- Cardiac Output (CO)
- Cardiac Index (CI)

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This trial will enroll Russian subjects with symptomatic chronic severe DMR and FMR per the MitraClip NT System IFU. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Screening

5.2.1 Subject Screening

The Principal Investigator at the site is responsible for screening subjects for the **MitraClip NT System** Russian Trial. All subjects must have a documented in-person consultation with the Cardiothoracic (CT) Surgeon investigator to assess surgical risk. The **MitraClip NT** implanter (who may also be the Principal Investigator) and a physician trained in echocardiography will also assess suitability of the subject for eligibility in the trial. These assessments combined are referred to as Site Heart Team. Refer below to the Table 1 for responsibilities.

Table 1. Responsibilities

Role / Specialty	**Responsibility**
Interventional Cardiologist	• Local Site Heart Team Member

CT Surgeon	• Screens potential subjects • Performs **MitraClip NT** procedure* • Local Site Heart Team Member • Provides in-person assessment of surgical difficulty
Physician trained on Echocardiography	• Local Site Heart Team Member • Evaluates potential subjects for echocardiographic eligibility criteria • Participates in the **MitraClip NT** procedure • Perform required analysis of the TEE & TTE to complete the Case Report Form (CRF)

Potential patients will be fully informed about the clinical investigation, following the established Informed Consent process (described in [Section 5.2.2]). Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin.

Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the CIP, and if applicable will be entered into a site-specific screening log.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records and on a screening log as required.

Subject data will be collected following enrollment into the clinical investigation.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical investigation. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and

thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

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

5.2.2.1 Special Circumstances for Informed Consent

Incapacitated subjects defined as mentally ill, mentally handicapped, or individuals without legal authority may be enrolled in this clinical investigation, as data of comparable validity cannot be obtained from clinical research involving only persons able to give informed consent or by other research methods. Additionally, the clinical investigation directly relates to a medical condition from which the individual suffers, and the clinical investigation is expected to produce a direct benefit to the individual, outweighing the risks and burdens involved.

Individuals under the age of 18 or age of legal consent are excluded from the study population.

Individuals unable to read or write may be enrolled in this clinical investigation.

Informed consent will be obtained through a supervised oral process. An independent witness will be present throughout the Informed Consent process. The written Informed Consent form and any other information will be read aloud and explained to the prospective subject or his/her legally acceptable representative and either will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained and that informed consent was freely given.

Pregnant or breastfeeding women are excluded from the study population.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL of the inclusion criteria to be

considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

5.3.2 Inclusion Criteria

5.3.2.1 General Inclusion Criteria

- Age 18 years or older.
- Symptomatic moderate-to-severe (3+) or severe MR (4+) chronic DMR or FMR determined by assessment of a qualifying transthoracic echocardiogram (TTE) obtained within 90 days or transesophageal echocardiogram (TEE) obtained within 180 days prior to subject registration.
- LVEF ≥ 30%
- NYHA classification is class II, class III, or ambulatory class IV.
- Subject is deemed difficult for mitral valve surgery due to either STS surgical mortality risk for mitral valve replacement of ≥ 8% OR due to the presence of one of the following risk factors:
  - Porcelain aorta or mobile ascending aortic atheroma
  - Post-radiation mediastinum
  - Previous mediastinitis
  - Functional MR with LVEF<40%
  - Over 75 years old with LVEF<40%
  - Re-operation with patent grafts
  - Two or more prior cardiothoracic surgeries
  - Hepatic cirrhosis
  - Other surgical risk factor(s)
- Mitral valve area ≥ 4.0 cm^2.
- The primary regurgitant jet is non-commisural, and in the opinion of the implanting investigator can successfully be treated by the MitraClip NT System. If a secondary jet exists, it must be considered clinically insignificant.

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

1. Subject is currently participating in another clinical investigation.
2. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period.
3. Patients with the following conditions:
   - Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen;
   - Active endocarditis of the mitral valve;
   - Rheumatic mitral valve disease;
   - Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus.
4. Contraindications for reusable accessories (stabilizer, lift, support plate).

5. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent

5.4.1 Subject Registration

A subject is considered registered when after enrolment and screening procedures it has been confirmed that the subject meets all inclusion criteria and none of the exclusion criteria and upon femoral vein puncture for transseptal access in preparation for the **MitraClip NT** System insertion.

5.6 Subject Withdrawal

Each enrolled subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation 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
- Subject's follow-up is terminated according to Section 3.1.

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

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

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

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall

make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

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

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

5.7 Number of Subjects

Sixteen (16) subjects will be registered in the clinical investigation.

5.8 Total Expected Duration of the Clinical Investigation

The expected duration of enrollment is 1 month. The expected duration of each subject's participation is 1 month, including the scheduled visits and data collection for this clinical investigation that will occur at 10 days and 30 days. Subjects will be exited from the trial at the conclusion of their 30-day follow-up visit. Therefore, the total duration of the clinical investigation is expected to be 2 months.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline/Pre-procedure/Pre-treatment

Transthoracic & Transesophageal Echocardiograms to Confirm Subject Eligibility
Eligibility assessments based on transthoracic echocardiogram (TTE) must be performed based on images obtained within 90 days prior to **MitraClip NT** procedure. Eligibility assessments based on transesophageal echocardiogram (TEE) must be performed based on images obtained within 180 days prior to procedure. Informed consent must be obtained prior to any non-standard of care assessments for trial eligibility.

Baseline Assessments
Once the patient has given the informed consent and was found to be suitable for inclusion in the study, the baseline assessment will be performed. If collected within past 30 days, the screening assessments may be used for the baseline information of the patient.

- Medical history
- Physical examination of the patient
- Evaluation by Local Site Heart Team

- Weight, temperature, blood pressure and heart rate
- Concomitant cardiac medications including dose
- CBC with differentials and platelet count
- Serum Creatinine
- Blood Urea Nitrogen (BUN)
- CK and CK-MB
- STS Mortality Risk Score for mitral valve replacement
- EuroScore II
- 12-lead ECG
- Transesophageal Echocardiography (TEE)
- Transthoracic Echocardiography (TTE)
- NYHA Classification
- Six Minute Walk Test (6MWT) distance
- Modified Rankin Scalea
- Estimation NT Pro-BNP

Anticoagulation and Antiplatelet

Discontinue the use of warfarin for at least three (3) days prior to the scheduled **MitraClip NT** procedure and ensure that the international normalized ratio (INR) ≤ 1.7. Similarly, discontinue dabigatran or factor Xa inhibitors for a sufficient duration to ensure restoration of normal coagulation. Subjects may be treated with heparin during this period at the treating physician's discretion. If heparin is used, it must be discontinued ≥ 4 hours prior to the **MitraClip NT** procedure for intravenous unfractionated heparin (UFH).

Administer a dose of ticlopidine, at a dosage determined by the Investigator, either just prior to, or immediately following the procedure. If a subject is already treated with other thienopyridine antiplatelet drug other than ticlopidine, it is not needed to replace the drug with ticlopidine.

Subject Preparation

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

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

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

MitraClip NT Procedure

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

Subjects are required to undergo an additional transesophageal (TEE) echocardiogram within 3 days prior to the procedure to rule out the presence of intracardiac mass, thrombus or vegetation. This echocardiogram may be performed immediately preceding initiation of the **MitraClip NT** procedure.

If a thrombus is identified, the subject may be pharmacologically treated to resolve the thrombus and, if successful, the subject may be reassessed for the clinical investigation.

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

The Steerable Guide Catheter (Guide) is inserted into the femoral vein and advanced across the transseptal puncture. Fluoroscopic and echocardiographic guidance will be used during the procedure to visualize the devices and the vasculature and cardiac anatomy. For subjects with renal dysfunction, intravenous contrast should not be used during the procedure unless absolutely necessary.

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

If MR reduction is not adequate, an additional **MitraClip NT** device may be placed at the implanter's discretion, depending on patient clinical condition, mitral valve area and mean Mitral Valve Gradient. A maximum of two (2) **MitraClip NT** devices may be implanted in subjects registered in this trial.

Post-MitraClip NT Procedure

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

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

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

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

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

The Investigator must instruct all subjects who receive the **MitraClip NT** device of the need for prophylaxis for endocarditis, as recommended in the guidelines for the prevention and treatment of infective endocarditis. Subjects must be instructed to notify the Investigator or the subject's primary care physician in the event that a procedure recommended by this Guideline is planned, so that prophylactic antibiotics can be prescribed. Post- **MitraClip NT** procedure anticoagulation is recommended per the Investigator's discretion as follows:

1. Reinitiate warfarin, dabigatran or factor Xa inhibitor (if discontinued for the **MitraClip NT** procedure) at pre-procedure levels or as appropriate. If chronic oral anticoagulation is used, then aspirin and ticlopidene use are not recommended, but are allowed if otherwise indicated for other conditions.
2. If chronic oral anticoagulation is not used, it is strongly recommended that either daily ticlopidence and/or aspirin (81 mg) is administered for 6 months or longer. If aspirin is to be used, a dose of 325 mg acetylsalicylic acid (ASA) may be administered either pre- or immediately post- **MitraClip NT** procedure followed by 81 mg per day for 6 months or longer per Institutional standards and at the discretion of the Investigator.

Follow-up for All Subjects

Clinical follow-up will be performed at the following intervals for all enrolled subjects, regardless of whether a **MitraClip NT** device was successfully implanted:

Discharge post- **MitraClip NT** procedure

- 10 days follow-up office visit (this visit must be conducted even if subject is in hospital);
- 30 days.
- Withdrawal or Discontinuation

All subjects should continue to be monitored and treated per applicable standards of care consistent with the subject's condition. Subjects implanted with the **MitraClip NT** device must also be evaluated for device integrity.

The follow up visits (discharge, 10 day, and 30 day) will include following assessments. Additionally, these assessments will also be collected before any withdrawal or discontinuation of a subject.

- Medical history
- Physical examination of the patient
- Weight, temperature, blood pressure and heart rate
- Concomitant cardiac medications including dose and reason(s) for any changes from Baseline
- CBC with differentials and platelet count
- Serum Creatinine
- Blood Urea Nitrogen (BUN)
- CK and CK-MB
- STS Mortality Risk Score for mitral valve replacement
- EuroScore II
- 12-lead ECG
- Transesophageal Echocardiography (TEE) – Screening, Discharge, 10 Days
- Transthoracic Echocardiography (TTE) – Screening, 10 Days, 30 Days
- NYHA Classification
- Six Minute Walk Test (6MWT) distance
- Modified Rankin Scalea
- Estimation NT Pro-BNP

Additional Follow-up Visits for All Subjects

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

- Adverse events
- Concomitant Cardiovascular Medications including dosage, including clinical reasons for any changes
- Hospitalizations
- Mitral valve surgery
- Additional **MitraClip NT** procedure(s)

Additional Interventions for MR Reduction

It may be necessary for a subject to undergo additional interventions for MR reduction such as an additional **MitraClip NT** procedure or mitral valve surgery.

Requirements for this visit are as follows:

- Medical history
- Physical examination of the patient
- Weight, temperature, blood pressure and heart rate
- Concomitant cardiac medications including dose and reason(s) for any changes from Baseline
- CBC with differentials and platelet count
- Serum Creatinine
- Blood Urea Nitrogen (BUN)
- CK and CK-MB
- STS Mortality Risk Score for mitral valve replacement
- EuroScore II

- 12-lead ECG
- Transesophageal Echocardiography (TEE)
- Transthoracic Echocardiography (TTE)
- NYHA Classification
- Six Minute Walk Test (6MWT) distance
- Modified Rankin Scalea
- Estimation NT Pro-BNP

Other scheduled follow-up visits from the date of the initial **MitraClip NT** procedure must be conducted.

6.2 Schedule of Events

Table 4.

		Screening/ Baseline	Discharge	10-D	30-D
Individual patient card	Medical history	×	×	×	×
	Physical examination of the patient	×	x	×	×
	Evaluation by Local Site Heart Team	×			
	Weight, temperature, blood pressure and heart rate	×	×	×	×
	Concomitant cardiac medications including dose and reason(s) for any changes from Baseline	x	×	×	×
	CBC with differentials and platelet count	×	x	x	×
	Serum Creatinine	×	x	x	×
	Blood Urea Nitrogen (BUN)	×	x	x	×
	CK and CK-MB	×	x	x	×
	STS Mortality Risk Score for mitral valve replacement	×	×	×	×
	EuroScore II	×	×	x	×
	12-lead ECG	×	×	×	×
	Transesophageal Echocardiography (TEE)	×	×	×	
	Transthoracic Echocardiography (TTE)	×		×	×
	NYHA Classification	×	x	×	×
	Six Minute Walk Test (6MWT) distance	×	×	×	×
	Modified Rankin Scalea	×	×	×	×
	Adverse events, hospitalizations, mitral valve surgery, additional intervention		x	×	×

	Estimation NT Pro-BNP	×	x	×	×

7.1 Adverse Events

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

The following ANTICIPATED EVENTS have been identified as possible complications of the MitraClip NT procedure:

Table 5.

• Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex) • Aneurysm or pseudo-aneurysm • Arrhythmias • Atrial fibrillation • Atrial septal defect requiring intervention • Arterio-venous fistula • Bleeding • Cardiac arrest • Cardiac perforation • Cardiac tamponade/Pericardial Effusion • Chordal entanglement/rupture • Coagulopathy • Conversion to standard valve surgery • Death • Deep venous thrombus (DVT) • Dislodgement of previously implanted devices • Dizziness • Drug reaction to anti-platelet/anticoagulation agents/contrast media • Dyskinesia • Dyspnea • Edema • Emboli (air, thrombus, MitraClip NT Device) • Emergency cardiac surgery • Endocarditis • Esophageal irritation	• Hemorrhage requiring transfusion • Hypotension/hypertension • Infection • Lymphatic complications • Mesenteric ischemia • Mitral stenosis • Mitral valve injury • MitraClip NT erosion, migration or malposition • MitraClip NT Device thrombosis • MitraClip NT System component(s) embolization • Multi-system organ failure • Myocardial infarction • Nausea/vomiting • Pain • Peripheral ischemia • Prolonged angina • Prolonged ventilation • Pulmonary congestion • Pulmonary thrombo-embolism • Renal insufficiency or failure • Respiratory failure/atelectasis/pneumonia • Septicemia • Shock, Anaphylactic or Cardiogenic • Single leaflet device attachment (SLDA) • Skin injury or tissue changes due to exposure to ionizing radiation • Stroke or transient ischemic attack (TIA)

• Esophageal perforation or stricture • Failure to deliver MitraClip to the intended site • Failure to retrieve MitraClip NT System components • Fever or hyperthermia • Gastrointestinal bleeding or infarct • Hematoma • Hemolysis	• Urinary tract infection • Vascular trauma, dissection or occlusion • Vessel spasm • Vessel perforation or laceration • Worsening heart failure • Worsening mitral regurgitation • Wound dehiscence

7.1 Definition

7.1.1 Adverse Event

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

Note 1: This definition includes events related to the medical device under investigation or the comparator.

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 medical devices under investigation.

7.1.2 Serious Adverse Event

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

a) Led to a death,
b) Led to a serious deterioration in health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalization or prolongation of existing hospitalization, or
    4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
    5. chronic disease
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

7.1.3 Device Deficiency/Device Malfunction

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

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

7.2 Device Relationship

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

7.2.1 Unanticipated (Serious Adverse) Device Effect

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

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled and registered in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. All adverse event data, including deaths and device deficiency data (if applicable), will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

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

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation.

All adverse events will be collected on each subject through the 30-day follow-up visit.

The following events are required to be reported for this study:

- All serious adverse events
- All cardiac events regardless of seriousness or device relationship
- All clinical investigation device-related events and events for which the relationship to the device under investigation is unknown
- All Cerebrovascular Accidents (CVAs).

The investigator should report all SAEs to the Sponsor or designee within 24 hours of site awareness.

In order to achieve timely reporting of SAEs, a copy of the completed CRF shall be sent to Sponsor and Designee. The email should be sent to **MitraClipRussia@abbott.com.**
The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB

The Sponsor requires the Investigator to report any USADE to the Sponsor or designee within 24 hours of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

7.3.3 Device Deficiency/Malfunction Reporting

All device deficiencies/malfunctions should be reported on the appropriate CRF form.

The investigator should report all device deficiencies/malfunctions to the Sponsor or designee as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor or designee no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

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

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

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor or designee will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 Statistical Considerations

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses may be maintained in a separate Statistical Analysis Plan (SAP).

8.1 Analysis Populations

FMR or DMR Russian patients who meet the eligibility criteria for the MitraClip NT System IFU in Russia, and registered into the study, defined in Section 5.4.1.

8.2 Rationale for Sample Size and Assumptions

Sixteen (16) DMR or FMR patients will be registered in the study. This sample size is determined based on the primary endpoint of successful implantation of the MitraClip NT device resulting in a decrease in the MR severity grade as assessed from the discharge echocardiogram.

[redacted]

Therefore, a sample size of 16 subjects ensure an observed rate that is readily interpretable.

[redacted]

8.3 Statistical Analysis

No pre-specified hypothesis tests are planned for this study. Descriptive analysis will be performed to summarize baseline, procedural, clinical data and primary and descriptive endpoints. 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, results will be summarized with the numbers of observations, means, standard deviations, and 95% confidence intervals for the mean. These calculations will be done under the assumption that the data are approximately normal in distribution.

For binary variables such as adverse events, results will be summarized with patient counts, percentages, and 95% confidence intervals.

8.4 Timing of Analysis

Timing of analysis is when all registered patients complete 30 days follow-up.

8.5 Subgroup Analysis

No subgroup analyses are planned for this clinical investigation.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. 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

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated for participation in the clinical investigation.

10.3 CIP Amendments

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

Acknowledgement/approval by the IRB/EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.4 Training

10.4.1 Site Training

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

10.4.2 Training Required for the Use of the Device

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

10.5 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

The Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations, and has the Clinical Trial Agreement.

- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP 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 monitor with a suitable working environment for review of clinical investigation-related documents.

10.6 Deviations from CIP

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

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

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

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

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

10.7 Quality Assurance Audit

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, 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 investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

11.0 DATA HANDLING AND RECORD KEEPING

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

CRF data collection will be performed on Paper Case Report forms. A copy of the completed and monitored CRFs will be collected by the Sponsor monitor for further data entry and data analysis.

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

11.1 Protection of Personally Identifiable Information

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

The Sponsor requires the investigational sites to transfer only key-coded data necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor will delegate data management and data analysis functions to an independent and accredited entity in the Russian Federation. This entity will handle the CRFs according to the applicable regulations in the Russian Federation and appropriately safeguard the collected information against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data entry and review. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. 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 clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF

11.4 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 CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor and/or Designee on the CRFs and in all required reports.

11.5 Record Retention

The Sponsor and/or Designee and Investigator/Site will archive and retain all documents pertaining to the clinical investigation 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 investigation records.

11.6 Investigational Devices Accountability

The Sponsor ships investigational products only to the Principal Investigator (the responsible leader of the investigational site) or his/her legal designee of each site, after sites receive documentation of site activation and shipping authorization is complete.

The Investigator or an authorized designee must maintain adequate records of the receipt and disposition of each investigational device, including part number, batch number, and serial number (if applicable), date used, subject identification, and treating physician.

Storage locations for the devices at investigational sites must be locked with access restricted only to investigators and authorized personnel.

12.0 ETHICAL CONSIDERATION

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at the investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to the institution's IRB/EC requirements.

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

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

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

13.1 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- the site is closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

The data and results from the clinical investigation 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 investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be

reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

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

15.0 Risk Analysis

Risks associated with the specified device and procedure, together with their likely incidence, are described in the IB/IFU. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

A risk management assessment was carried out and documented in the framework of the main plan and risk management report, including:

1. Hazard analysis for each device;
2. Purpose of the device and characteristics affecting safety;
3. Potential hazards;
4. Potential clinical harm and associated serious consequences;
5. Ratio Analysis of clinical risk and benefit.

An analysis of the types and consequences of failures was developed for assessing the risks associated with a medical device in order to determine whether it can be used for its intended purpose.
As part of the procedure, the manufacturer identified the hazards associated with the use, design and procedures. Hazards with an unacceptable level of risk have been reduced to an acceptable level by changing the design, testing, and other mutually acceptable measures.
Currently, the manufacturer uses a procedure to assess the severity of clinical risks on a scale from minor to critical risks. If unacceptable levels of the risk index were identified, measures were needed to reduce the risks.
Based on the analysis, all identified and foreseeable hazards and associated risks were identified and reduced to acceptable levels.
The requirements for risk management comply with the essential requirements of Annex I to Council Directive 93/42 / EEC on medical devices.

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