Evaluation of the 5-year Safety and Performance of the Medtentia Annuloplasty Ring in Adults - Follow-up to Clinical Investigation 2010-040

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CIP Version: Final 1.0

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CLINICAL INVESTIGATION PLAN

Evaluation of the 5-year Safety and Performance of the Medtentia Annuloplasty Ring in Adults - Follow-up to Clinical Investigation 2010-040

Clinical Investigation Code:	2010-040FU5
Version Number:	Final 1.0
Release Date:	08-May-2019
Investigational Medical Device:	Medtentia Annuloplasty Ring (MAR)
Sponsor:	Medtentia International Ltd Oy [redacted]
Sponsor‘s Representative:	[redacted]

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Sponsor Signature Page

Clinical Investigation Code: 2010-040FU5

Clinical Investigation Plan reviewed and approved by:

Chief Executive Officer

Name	Signature	Date

Head of Quality Assurance

Name	Signature	Date

Consultant Signature Page

Clinical Investigation Code: 2010-040FU5

Clinical Investigation Plan prepared by:

Medical Writer

[redacted]

[redacted] | Signature | Date

Statistician

[redacted]

[redacted] | Signature | Date

Clinical Investigation Plan Agreement Form

Clinical Investigation Code: 2010-040FU5

I agree to the terms of this Clinical Investigation Plan. I will conduct the investigation according to the procedures specified herein.

Principal Investigator:

[redacted]

Signature Date

Site:

[redacted]

INVESTIGATION SITES

Principal Investigator:

[redacted]

Site name and address:

[redacted]

1. SYNOPSIS

Title	Evaluation of the 5-year Safety and Performance of the Medtentia Annuloplasty Ring in Adults - Follow-up to Clinical Investigation 2010-040
Sponsor	Medtentia International Ltd Oy
Name of IMD	Medtentia Annuloplasty Ring (MAR)
Indication	Patients with mitral valve (MV) regurgitation requiring annuloplasty repair of their native MV with retention of the natural valve apparatus and normal valve orifice, remodeling of the annulus and prevention of secondary distension after valvuloplasties
Purpose of the Investigation	The purpose of this clinical investigation is to evaluate long-term safety and performance of the MAR in patients who underwent successful mitral valve surgery using Medtentia's MAR system in clinical investigation 2010-040 performed during June 2011 - April 2016
Design	Observational, single-center
Subject Population	11 subjects, who underwent MV repair operation with successful MAR implantation in clinical investigation 2010-040
Objectives	The primary objective of this clinical investigation is to evaluate long-term performance and safety of MAR five years after mitral valve repair surgery
Subject Selection	**Inclusion Criteria** Subjects who participated in the clinical investigation 2010-040 and meet ALL of the following inclusion criteria are eligible for participation

	in this investigation: 1. Signed Informed Consent Form 2. Subject had a successful MAR implantation in clinical investigation 2010-040 3. Subject is willing to participate in the follow-up study and to comply with the requirements of the CIP **Exclusion Criteria** Subjects who participated in the clinical investigation 2010-040 but had the MAR replaced with another MV repair ring or system are not eligible for participation in this investigation
Investigation Procedures	**Visit** After signing the Informed Consent Form, the subjects will have the following assessments: • Demographics • Relevant medical history after the last follow-up visit (2 years after MAR implantation) of investigation 2010-040 • Assessment for functional mitral regurgitation as defined by current American College of Cardiology/American Heart Association (ACC/AHA) guidelines • Vital signs (pulse, blood pressure, and body temperature) and weight • New York Heart Association (NYHA) rating • Electrocardiography (ECG) • Quality of Life Questionnaire (15D©) • Trans-thoracic echocardiography (TTE)
Data Analysis and Statistics	**Definition of the analysis populations** Long-term follow up data of 11 subjects, who underwent MV repair operation with successful MAR implantation in clinical investigation 2010-040 performed during June 2011 - April 2016

	Statistical methods A statistical analysis plan (SAP) detailing the statistical analyses will be written and finalized prior to final data analyses Qualitative and quantitative statistics will be used, as appropriate, to present and summarize the data collected in the clinical investigation
Endpoints	**Primary safety endpoints** The occurrence, nature and frequency of significant medical events since the last visit of clinical investigation 2010-040 as defined in section 8.4 of this Clinical Investigation Plan **Primary performance endpoints** Change in MR from the 2-year follow-up data point to the 5-year follow-up as measured by TTE. Success will be defined as no change or any improvement in MR class as described in the ACC/AHA Guidelines. **Secondary endpoints** **<u>Safety</u>** • All-cause mortality collected retrospectively since the last visit of clinical investigation 2010-040 • The occurrence, nature and frequency of adverse device effects (ADEs) and/or device deficiencies (DDs) since the last visit of clinical investigation 2010-040 • Number of cardiovascular admissions occurred since the last visit of clinical investigation 2010-040 **<u>Other Safety</u>** • The number of subjects with clinically significant abnormal findings in TTE, ECG, or vital signs and type of abnormal findings will be listed and tabulated

	Performance • Change from the clinical investigation 2010-040 2-year follow-up in the following MR parameters, as measured by TTE: - Left ventricle reverse remodeling (standard measurement points) - Coaptation height • Changes in NYHA classification when compared to the clinical investigation 2010-040 2-year follow-up visit. • Number of subjects with recurrence of MR defined as changing of MR to moderate or severe according to ACC/AHA classification determined by TTE. **Other** • Number of subjects with re-operation or MV reintervention due MAR performance failure or malfunction • Quality of life scores as measured by the 15D©questionnaire.
Data Collection	Data will be collected using Electronic Data Capture (EDC) system.
Investigation Duration	The investigation duration for each individual subject includes only one visit. Subjects will undergo interview and assessments specified in this CIP Estimated overall study duration from first subject first visit to last subject last visit May-June 2019

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2. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACC	American College of Cardiology
ADE	Adverse device effect
AE	Adverse event
AHA	American Heart Association
ASADE	Anticipated serious adverse device effect
CE	Conformite Europenne (Conformity Mark for products marketed in the European Economic Area)
CI	Confidence interval
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
EC	Ethics Committee
ECHO	Echocardiography
ECG	Electrocardiography
eCRF	Electronic case report form
EDC	Electronic data capture
ERO	Effective regurgitant orifice area
ESC	European Society of Cardiology
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IMD	Investigational medical device
ISF	Investigator Site File
ISO	International Organization for Standardization
LV	Left ventricle
LVEF	Left ventricle ejection fraction
MAR	Medtentia Annuloplasty Ring
MEDDEV	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Authorities
MR	Mitral regurgitation
MV	Mitral valve
NYHA	New York Heart Association
RA	Regulatory authority
SADE	Serious adverse device effect
SAE	Serious adverse event
TTE	Trans-thoracic echocardiography

3. BACKGROUND AND RATIONALE

3.1 Background Information

Mitral regurgitation (MR) is an abnormal flow of blood in the heart from the left ventricle back to the left atrium caused by an incomplete closure of the mitral valve (MV) (Cooper *et al.*, 1998). MR can result either from a structural or degenerative abnormality of the MV itself, or a distortion of the architecture or function of the left ventricle. With an estimated global prevalence of 1.7% and over 10% in people aged ≥75, MR is the most common heart valve disease (Nkomo *et al.*, 2006; Mozaffarian *et al.*, 2016; Nishimura *et al.*, 2016).

Initially patients with MR may have no symptoms because of compensatory changes to the heart. If MR is left untreated, compensatory changes to the heart become irreversible (Nishimura *et al.*, 2016). The severity of MR usually worsens gradually, and severe MR eventually leads to left ventricular failure, various cardiac morbidities, and death if left untreated (Pozzoli *et al*., 2016). 90% of patients with severe MR end up dying or requiring cardiac surgery within 10 years of diagnosis (Enriquez-Sarano *et al.*, 2009).

There are currently no generally accepted pharmacological treatments for MR. Surgery has been the only treatment truly improving patient outcomes, especially over the long term (Vahanian *et al.*, 2012). Therefore, the surgery is strongly recommended in the case of severe or moderate MR, as well as in asymptomatic patients in the case of progressive cardiac enlargement visible by ECHO (Falk *et al.*, 2017; Iung *et al.*, 2002). Surgical intervention aims either at repairing the MV or at replacing it with an artificial valve (Nishimura *et al.*, 2016). Surgical MV repair, or MV annuloplasty, involves an annuloplasty ring that is implanted around the MV annulus, thus supporting the coaptation of the leaflets. Timely MV annuloplasty often associates with a good clinical outcome and normalized lifetime expectancy (De Bonis *et al.*, 2016; Pozzoli *et al.*, 2016). MV repair has been estimated to be clinically superior to valve replacement surgery and is therefore the preferred option (Jokinen *et al.*, 2007; Nishimura *et al.*, 2016; Pedrazzini *et al.*, 2010; Shang *et al.*, 2017; Zhou *et al.*, 2010).

The MV repair process, however, is both technically demanding and time-consuming: it usually requires careful placement of more than ten sutures, and experienced and multidisciplinary operators are required to obtain good outcomes (LaPar *et al.*, 2014; Nishimura *et al.*, 2016). The Medtentia Annuloplasty Ring (MAR) was designed to provide a simpler alternative for the current technically demanding mitral repair processes. In preclinical safety and efficacy studies conducted in sheep, the new MAR system has proven to be easy to use, well tolerated, and to have a functional outcome comparable to that of a certified annuloplasty ring. MAR was also

proven to effectively stop MR without causing thrombus formation or hemolysis (Jensen *et al.*, 2010; Konerding *et al.*, 2013). Furthermore, MAR rings were temporarily positioned in 18 patients undergoing otherwise conventional annuloplasty and then removed without incident before the annuloplasty continued (Medtentia International Ltd Oy, 2011). No safety issues were seen when annuloplasty using the MAR was performed in these studies.

During the years 2011-2014, MAR was implanted to 11 patients needing mitral valve regurgitation correction (investigation code: 2010-040) at two study stages. The outcomes of the study are presented in detail in the Clinical Investigation Report, dated 14-Feb-2019. As a conclusion this clinical investigation showed the first clinical evidence on MAR being an effective and well-tolerated method for the treatment of MR.

This follow-up study to evaluate the 5-year performance and safety of the MAR in the current subject population is expected to provide valuable insight into the longer-term performance and safety of the MAR.

3.2 Summary of Clinical Data Preceding the Follow-up Clinical Investigation (2010-040)

The prospective, single-arm clinical investigation was conducted between 2011–2014 (clinical investigation code: 2010-040), which aimed at investigating the safety and performance of MAR in subjects with MR requiring mitral valve annuloplasty.

A total of 11 subjects with severe MR underwent successful mitral valve annuloplasty with MAR during two stages of this clinical investigation and were regularly followed up to 2 years after the surgery. At Stage 1 MAR Classic sizes available were 28-36 mm in 2 mm increments. At Stage 2, MAR Regular and Expanded sizes available were 26-40 mm diameters in 2 mm increments; Regular and Expanded corresponded to mitral leaflet's thicknesses.

During the first stage 17 subjects requiring mitral valve repair surgery were screened between June 2011 and August 2012. Implantation of the MAR was not attempted for one of these subjects, whose anterior leaflet was determined to be too large. MAR implantation was attempted but not completed for 9 subjects. Of these, three had thickened leaflets, two in addition to thick leaflets also had myxomatous mitral valve, one had annulus too small for the ring sizes defined in clinical investigation plan and available at that time, three had other anatomical features that made implantation unfeasible. Annuloplasty was completed using the MAR in the remaining 8 subjects, for one of these unsuccessfully leading to the replacement of MAR with a smaller Physio Ring. For one subject re-operation had to be done after few days due to continuous moderate-to-severe regurgitation and the MAR was replaced with a smaller Physio Ring. In total, the successful annuloplasty was completed using MAR (Classic) for 6

subjects during the Stage 1. As planned in the CIP, enrollment was then halted to allow a safety review by an independent data safety monitoring board (DSMB) composed of two clinicians with expertise in MV repair surgery and a biostatistician after the 6-month follow-up of the last of these subjects.

On 04-Feb-2013 DSMB reviewed the Stage 1 data and found no safety concerns thus concluding that it was ethical and feasible to continue the study as planned (Lauer *et al.*, 2013).

As a consequence of the unexpectedly high number of patients with thickened leaflets, slight modifications were made to the ring design before the Stage 2 was opened for recruitment. A greater diversity of MAR sizes and an additional version of the MAR with a wider distance between the loops allowing implantation in patients with thicker mitral leaflets became available for Stage 2. Stage 2 started in July 2013, and the first implantation occurred on 10-Jul-2013. By May 2014, 5 subjects were successfully implanted with MAR and 2 were withdrawn due to anatomical anomalies. In August 2014 the project development was put on hold for a year. The company decided to terminate the study in September 2015 due to company's focus shift towards the development of a transcatheter technology for mitral regurgitation and strategical reasons. No new subjects were enrolled after June 2014.

Due to the limited number of subjects, the decision was made to use only descriptive statistics for data analysis.

MAR performance results showed that at the 3-month time point, MAR implantation had induced a 2-degree MR status improvement in 10 out of 11 subjects (90.9%; 95% CI 58.7–99.8%). Two years after surgery, MR status had improved by at least 2 degrees in all 11 subjects (100%; 95% CI 71.5–100). Improved score according to NYHA classification also confirmed that all subjects with MAR had benefited from the operation: all had normal mitral leaflet motion and diminished size of the left ventricle two years after the MAR implantation. Reverse remodeling of the left ventricle after MAR implantation led to recovery of the anatomical features of the MV in all subjects who underwent a successful surgery. Hence, after the two-year follow-up period defined by the 2010-040 study design, all MAR subjects had diminished left ventricle size. The improved MR result was further supported by the NYHA assessment of subjects' heart failure status that is based on an interview evaluating how much the potential heart condition limits the study subject's physical activity. Two years after MAR implantation, all subjects had reached class I functional classification and thus had no limitations of physical activity caused by their heart condition.

No deaths occurred in the hospital or during the 24-month follow-up. No device-related adverse events (ADEs) were detected in the subjects eligible for the study.

Regarding the safety of MAR and the implantation procedure, total number of non-device related AEs was 31. Of these, one event was major adverse cardiac event (MACE) - residual regurgitation leading to reoperation was observed on a 75-year-old female subject who had been excluded from the MAR population due to the concomitant annular decalcification. The MACE was deemed to be due to the small size and overall fragility of the subject's mitral annulus, for which the MAR size used (32mm) could have been suboptimal, and it led to reoperation of the subject and MAR removal four days after the operation. No increases in the subjects' mean thrombocyte values were detected during the study, indicating low thrombogenicity of the MAR.

Thirteen serious adverse events (SAE) were reported: 11 SAEs had occurred after the MAR operation and two occurred post operation before the subject was released from the hospital – all resolved during the investigation; 6 of 14 SAEs were cardiology related (including MACE). Two SAEs were both severe and classified as MAR procedure related (one related and one possibly related).

This clinical investigation results showed that mitral valve annuloplasty with the MAR is a well-tolerated and efficient method to treat patients suffering from severe mitral regurgitation.

3.3 Risks and Anticipated Adverse Device Effects to Be Assessed

This is an observational follow-up clinical investigation.

There were no adverse device effects (ADEs) nor serious ADEs (SADEs) in previous clinical investigation 2010-040.

4. INVESTIGATIONAL MEDICAL DEVICE INFORMATION

Medtentia Annuloplasty Ring (Classic, Regular, and Expanded) and its accessories for selecting and implanting an appropriate mitral annuloplasty ring were used during the clinical investigation 2010-040.

The following disposition of investigational device type and ring sizes were during the clinical investigation 2010-040:

- At Stage 1 (year period 2011-2012), MAR Classic sizes were 28-36 mm in 2 mm increments.

- At Stage 2 (year period 2013-2016), MAR Regular and Expanded sizes were 26-40 mm diameters in 2 mm increments; Regular and Expanded corresponded to mitral leaflet's thicknesses.

Details on the device and its manufacturing process of the MAR can be found in the most recent Investigator's Brochure (IB) (Medtentia International Oy, 2019).

5. RISK EVALUATION

5.1 Risks Associated with the Participation in the Clinical Investigation

Medtentia International Ltd Oy does not foresee any risks associated with this investigation.

5.2 Risk/Benefit Assessment

This is an observational follow-up clinical investigation. There are no additional risks anticipated, specific to participating in this study for the subjects. The investigation is not examining any experimental procedures and participation in the investigation is not predicted to affect the medical treatment received by enrolled subjects.

There is minimal potential for direct benefit to subjects as the investigation does not involve any change to their standard monitoring and treatment. However, there may be a benefit in the special attention paid to the subjects' cardiac function and picking up additional information from the subjects' assessment.

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1 Purpose

This clinical investigation is a continuation of the clinical investigation 2010-040 aiming to assess the long-term outcomes of the surgical therapy of MR using MAR. The purpose of this clinical investigation is to evaluate 5-year safety and performance of the MAR in patients who underwent successful mitral valve surgery using Medtentia's MAR system in the clinical investigation 2010-040 performed during June 2011 - April 2016.

6.2 A description of the study design including justification based on clinical evaluation

A pilot clinical investigation 2010-040 was conducted at the Helsinki University Central Hospital between June 2011 and April 2014. During two study stages of this clinical investigation MAR was implanted for 12 subjects. 11 of 24 consented subjects did not receive the device due to non-anatomical fit, mainly at Stage 1, therefore after sizing adjustment of the implant (Regular and Expanded) the enrolment rate improved significantly. For 1 subject MAR was replaced

before the operation was completed. For 1 subject the implantation was successful, but four days post-operation, MAR had to be replaced with another ring type due to the mismatch of the ring size. This emphasizes the importance of various ring sizes, as well as careful evaluation of patient's mitral valve anatomy before a MAR operation.

11 of 12 of the MAR population recovered from operation with improved mitral regurgitation and were regularly followed up to 2 years of ring implantation. The primary safety endpoints of the clinical investigation were met with no device-related safety issues and 100% survival. The primary performance endpoints were met with mitral regurgitation improvement of at least 2 degrees in mitral regurgitation class.

The limitations of clinical investigation 2010-040 include relatively small subject population, as well as the relatively short follow-up time for a surgical product. Therefore, an observational follow-up study to evaluate the 5-year performance and safety of the MAR in the current subject population was planned.

This follow-up study, 2010-040FU5, aims to include 11 MAR subjects for one follow-up visit in order to evaluate whether MAR has been able to keep the mitral regurgitation trivial or mild. Subjects are planned to enter this follow-up clinical investigation at least 5 years after MAR implantation.

The sponsor selected [redacted] hospital as a follow-up clinical investigation site based upon a site assessment considering appropriate facilities, qualifications of the investigators' experience with the intended procedures, and ability to conduct the study according to the clinical investigation plan.

6.3 Randomization and Blinding/Masking

This section is not applicable.

6.4 Objectives and Endpoints

6.4.1 Primary Objectives

Safety

- To evaluate the safety of the MAR in terms of longstanding complications and adverse events

Performance

- To evaluate the performance of the MAR 5 years post MV repair surgery

6.4.2 Secondary Objectives

Safety

- To evaluate the safety of the MAR in terms of survival since the last visit of clinical investigation 2010-040

Performance

- To obtain additional performance information

6.4.3 Primary Endpoints

Safety

- The occurrence, nature and frequency of significant medical events since the last visit of clinical investigation 2010-040 as defined in section 8.4

Performance

- Change in MR from the 2-year follow-up data point to the 5-year follow-up as measured by TTE. Success will be defined as no change or any improvement in MR class as described in the American College of Cardiology/ American Heart Association (ACC/AHA) Guidelines

6.4.4 Secondary Endpoints

Safety

- All-cause mortality collected retrospectively since the last visit of clinical investigation 2010-040
- The occurrence, nature and frequency of adverse device effects (ADEs) and/or device deficiencies (DDs) since the last visit of clinical investigation 2010-040
- Number of cardiovascular admissions occurred since the last visit of clinical investigation 2010-040

Other Safety

- The number of subjects with clinically significant abnormal findings in TTE, ECG, or vital signs and type of abnormal findings will be listed and tabulated

Performance

- Change from the clinical investigation 2010-040 2-year follow-up in the following MR parameters, as measured by TTE:

- Left ventricle reverse remodeling (standard measurement points)
- Coaptation height

- Changes in NYHA classification when compared to the clinical investigation 2010-040 2-year follow-up visit.
- Number of subjects with recurrence of MR defined as changing of MR to moderate or severe according to ACC/AHA classification determined by TTE.

Other

- Number of subjects with re-operation or MV reintervention due MAR performance failure or malfunction
- Quality of life scores as measured by the 15D© questionnaire.

6.5 Anticipated AEs to be Assessed

In the clinical investigation 2010-040 a favorable safety and tolerability profile has been demonstrated for MAR. The most frequently reported AE was atrial fibrillation. The overall number of reported SAEs were 14, of these 6 SAEs were of cardiac disorders group.

Based on the safety profile from the 2010-040 investigation, there were no ADEs, nor SADEs reported. AEs in the class of cardiac disorders may be expected

For additional details on the safety and efficacy of MAR, please refer to the Investigator's Brochure.

6.6 Clinical Investigation Materials and Equipment

Medtentia International Ltd Oy will control the supply of the latest version of the Clinical Investigation Plan and all other materials required to conduct the clinical investigation.

TTE, ECG and blood pressure measurements will be performed with hospital equipment and used within standard of care. Maintenance and calibration of the equipment is the responsibility of the investigation site and will be performed per hospital procedures.

The clinical research associate (CRA) will verify that the site has applicable maintenance and calibration documents for these devices prior the subject enrolment.

6.7 Subject Enrollment

The sample size will be determined by the number of qualifying subjects from the clinical investigation 2010-040 who can be located and who agree to participate in this follow-up

investigation. Subjects who underwent successful MAR implantation and completed 2010-040 clinical investigation will be contacted and invited to participate in the follow-up study. Maximum of 11 subjects is anticipated to be enrolled in this follow-up clinical investigation.

6.8 Control

This section is not applicable.

6.9 Duration of Participation

The maximum duration of each subject's participation in this observational investigation corresponds to the length on the study single visit, which expected to be approximately 3 hours. The point of enrollment is considered to be the time point at which the subject signs the Informed Consent Form (ICF).

6.10 Time Schedule

The follow-up investigation visits for the 11 MAR patients will be occurring during May to June 2019. The end of the clinical investigation is defined as the date of the last visit of the last subject in the investigation.

7. INVESTIGATION POPULATION

The aim is to enroll the subjects, who underwent MV repair operation with successful MAR implantation in clinical investigation 2010-040.

7.1 Inclusion and Exclusion Criteria

The Investigator must ensure that the enrolled subjects who participated in the clinical investigation 2010-040 meet all the following inclusion criteria:

1. Signed Informed Consent Form.
2. Subject had a successful MAR implantation in clinical investigation 2010-040.
3. Subject is willing to participate in the follow-up study and to comply with the requirements of the CIP.

Exclusion criteria

Subjects who participated in the clinical investigation 2010-040 but had the MAR replaced with another MV repair ring or system are not eligible for participation in this investigation

7.2 Discontinuation or Withdrawal Criteria

This clinical investigation consists of one visit only, therefore discontinuation or withdrawal of the subject by the Investigator is not expected.

8. STUDY PROCEDURES

8.1 Informed Consent

The subject may only be included in the follow-up study after providing written informed consent as described in Section 11.1 Informed Consent. Failure to obtain signed informed consent renders the patient ineligible for the study.

8.2 Subject Number

The following series of numbers and letters will comprise the Subject Identification Code (SIC):

CIP code (2010-040FU5) and 3-digit subject number (e.g., 001), which will be retained as was assigned in the clinical investigation 2010-040.

8.3 Visit Schedule and Assessments

During the follow-up study each subject will visit the site only once.

The Investigator will conduct the informed consent process (section 11.1), ensuring that the subject's signature has been obtained on the ICF and that the subject has received a copy before any study specific procedures are conducted. Once the ICF is signed, the Investigator will perform the following assessments:

- Collection of subject's demographics
- Recording any relevant medical history after the last follow-up visit (2 years after MAR implantation) of the clinical investigation 2010-040
- Recording whether the subject had functional mitral regurgitation as defined by current ACC/AHA guidelines
- Vital signs (pulse, blood pressure, and body temperature) and weight
- New York Heart Association (NYHA) rating
- ECG
- Quality of Life Questionnaire (15D©)
- TTE

8.3.1.1 Demographics

Demographic data will be collected: date of birth, age, sex, race, and smoking habits.

8.3.1.2 Medical history

At the visit the subject's medical history will be documented including significant medical events, defined as events of cardiovascular origin and events fulfilling ADE and DD criteria, experienced since the last visit in the clinical investigation 2010-040.

8.3.1.3 Assessment for functional mitral regurgitation

The symptoms will be collected from the subjects and TTE values in order to assess whether subject had functional mitral regurgitation as defined by current ACC/AHA guideline.

8.3.1.4 Vital signs

Vital signs will be recorded using standard equipment available at the site. Parameters to be measured at the visit include pulse, systolic and diastolic blood pressure, body temperature and weight. Pulse and blood pressure will be measured after the subject has been in a resting position for at least five minutes and repeated three times. The average value will be entered in eCRF. Weight will be measured in indoor clothing, but without shoes. All measurements will be recorded directly in the eCRF. Investigator will be asked to comment on any clinically significant abnormalities.

8.3.1.5 Assessment of heart failure status

The status of each subject will be assessed according to the NYHA scale.

8.3.1.6 Electrocardiography (ECG)

A 12-lead ECG will be performed and the print-outs will be evaluated by the Investigator. Any clinically significant abnormality will be recorded in eCRF.

8.3.1.7 Transthoracic echocardiography (TTE)

TTE will be performed using the same standardized method described in detail in a separate Echocardiography Imaging and Submission Guidelines, version 2.0, dated 11-Jun-2013, as used in the main study 2040-040. TTE results will be documented in the subjects' charts and eCRF.

Mitral regurgitation will be assessed during the TTE.

The following parameters will be assessed:

- MR class (classes I – IV), according to the ACC/AHA classification
- Coaptation height (mm)

- Left ventricle remodeling (standard measurement points, mm)
    - LV end systolic diameter
    - LV end diastolic diameter
    - Left ventricle ejection fraction (LVEF)
- Venae contracta (mm)
- Mitral valve peak gradient (mmHg)
- Regurgitant volume (ml)
- Effective Regurgitant Orifice Area (cm^2)

8.4 Adverse Events, Adverse Device Effects and Device Deficiencies

This is an observational follow-up study, consisting only of one visit. Significant medical events will be considered as events of cardiovascular origin and other events fulfilling, ADE and DD criteria. These events will be collected from the subject retrospectively from the timepoint of the last visit in the clinical investigation 2010-040.

It is of utmost importance that all staff involved in the investigation are familiar with the definitions and procedures and it is the responsibility of the Investigator to ensure this.

Adverse Event (AE)

Adverse Events are defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal laboratory finding), in subjects, users or other persons whether or not considered related to the investigational medical device.

Note 1: This definition includes events related to the investigational medical device.

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

Note 3: For users or other persons, this definition is restricted to events related to the investigational medical device

Adverse Device Effect (ADE)

Adverse event related to the use of the investigational medical device.

Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instruction for use, or any malfunction of the investigational medical device.

Note 2: This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Event (SAE)

Adverse Event that:

1. Leads to a death, injury or permanent impairment to a body structure or body function
2. Leads to a serious deterioration in the health of the subject, that either resulted in:

a. a life-threatening illness or injury or

b. a permanent impairment of a body structure or a body function, or

c. in-patient hospitalization or prolonged hospitalization,

d. in medical or surgical intervention to prevent life-threatening illness

3. Leads to fetal distress, fetal death or a congenital abnormality or birth defect

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report.

Device Deficiency (DD)

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.

8.4.1 Significant Medical Events

Due to the nature and regulatory strategy of this investigation, the scope of adverse event reporting in this investigation has been limited to collection and reporting of the following significant medical events:

- Significant medical events according to the Table 1.

- Any Device Deficiency (DD) that might have led to a SAE if (a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. DD relates to inadequacy of an investigational medical device related to its identity,

quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Regulatory authorities and EC will be informed about the retrospective events in the final report to be written in the end of this investigation.

The Investigator must record any of the events listed in the Table 1, regardless of relationship to the investigational medical device, and any DD that might have led to a SAE in the eCRF. Each unique event or diagnosis must be documented separately. Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

Table 1. Significant medical events required to be collected and reported by the Investigator (the list is based on standardized event reporting and data collection recommendations, Hicks et al. 2014 and 2017)

Event	**Description**
Death	- Cardiovascular - Non-cardiovascular - Undetermined cause of death
Heart failure	Presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of heart failure
Myocardial infarction	
Hospitalization	For cardiovascular causes
Stroke or another cerebrovascular event	Should be assessed by a neurologist and CT/CMR imaging Severity should be documented: - Disabling - Nondisabling
Percutaneous coronary intervention	It is defined as the placement of an angioplasty guidewire, balloon, or other device into a native coronary artery or CABG for the purpose of mechanical coronary revascularization The assessment of coronary lesion severity by intravascular ultrasonography, coronary flow reserve, or fractional flow

	reserve is not considered a percutaneous coronary intervention procedure
Peripheral vascular intervention	It is defined as a catheter-based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits
Arrhythmias and conduction system disturbances	
Unplanned cardiac surgery for any cause	When a surgery is performed after implantation of a device, a new or worsened disease state that prompted the surgery is coded as the event, not the surgery itself.
Specific device-related technical failure issues and complications	

Classification of Causal Relationship

For each reported event, the causal relationship between the event and the investigational device will be classified as related, not related or unknown. At this long-term assessment of the MAR the causal relationship with implant procedure is considered not applicable.

The event should be considered as not device related if it could be expected to occur even when the device performs at 100% of expectations.

Classification of Severity

Severity of each reported event will be assessed using the following definitions:

Mild: aware of sign or symptom, but easily tolerated.

Moderate: discomfort enough to cause interference with usual activity.

Severe: incapacitating with inability to work or do usual activity.

8.4.2 Medical Care

After participation in a clinical investigation the subject will be advised or referred by the Investigator for a medical care according to national guidelines.

9. STATISTICS

9.1 General Statistical Considerations

Descriptive statistics will be used to present and summarize the data collected in the clinical investigation. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, median and maximum value. Categorical data will be presented as counts and percentages.

Any deviations from this section and/or the Statistical Analysis Plan (SAP) will be described and justified in the Final Clinical Study Report, as appropriate.

9.2 Statistical Methods

A statistical analysis plan detailing the statistical analyses will be written and finalized prior to final data analyses.

9.2.1 Primary Endpoints

9.2.1.1 Safety

The occurrence, nature and frequency of significant medical events since the last visit of clinical investigation 2010-040 as defined in section 8.4 will be listed and tabulated.

9.2.1.2 Performance

The percentage of subjects with stable MR condition or any improvement in MR class as described in the ACC/AHA Guidelines 5 years after MAR implantation will be calculated with its two-sided 95% CI (if applicable).

9.2.2 Secondary Endpoints

9.2.2.1 Safety

All-cause mortality collected retrospectively since the last visit of clinical investigation 2010-040 will be summarized in a frequency table.

The occurrence, nature and frequency of adverse device effects (ADEs) and/or device deficiencies (DDs) since the last visit of clinical investigation 2010-040 will be summarized.

Number of cardiovascular admissions occurred since the last visit of clinical investigation 2010-040 will be summarized.

Descriptive statistics with two-sided 95% CIs, when appropriate, will be presented for all safety data for the MAR population.

9.2.2.2 Other Safety

The number of subjects with clinically significant abnormal findings in TTE, ECG, or vital signs and type of abnormal findings will be listed and tabulated.

9.2.2.3 Performance

The MR parameters left ventricle reverse remodeling (standard measurement points) and coaptation height will be tabulated using descriptive statistics. For the same parameters, a comparison with the clinical investigation 2010-040 2-year follow-up visit will be presented by absolute change and %-change. The changes in MR parameter values may also be analyzed graphically.

The Changes in NYHA classification when compared to the clinical investigation 2010-040 2-year follow-up visit will be summarized.

The number of subjects with recurrence of MR defined as changing of MR to moderate or severe according to ACC/AHA classification determined by TTE will be tabulated.

The percentage of subjects with recurrence of MR from 2-year follow-up visit will be calculated with their two-sided 95% CI.

9.2.2.4 Other

Number of subjects with re-operation or MV reintervention due MAR performance failure or malfunction will be summarized.

Quality of life scores as measured by the 15D©questionnaire will be summarized.

9.3 Reporting of Deviations

Any deviations will be collected to a deviation log by the study monitor and listed by subject in the final report.

9.4 Missing, Unused and Spurious Data

The handling of missing data will be detailed in the Statistical Analysis Plan.

9.5 Datasets to Be Analyzed

The Medtentia Annuloplasty Ring population (MAR population) consists of subjects, who underwent MV repair operation with successful MAR implantation in clinical investigation 2010-040. All analysis will be performed on the MAR population.

9.6 Demographic and Baseline Characteristics

Subject disposition, demographic and other baseline data will be presented using summary statistics and data from subjects in the MAR population.

9.7 Number of Subjects

11 subjects with MAR implanted will participate in this follow-up study.

10. DATA AND QUALITY MANAGEMENT

10.1 Site Monitoring

The study will be monitored in compliance with the Declaration of Helsinki, ISO 14155:2011, the CIP, all applicable national and local regulations and according to [redacted] standard operating procedures (SOPs). All monitoring activities will be conducted by a trained and qualified monitor who will document each monitoring visit. In general, during monitoring visits, the monitor will make sure the informed consent procedure has been appropriately carried out and will compare the eCRF entries to original source data at the investigation site. All data must be accurately recorded in the eCRF.

Authorized representatives of the Sponsor and/or regulatory authorities may visit the site to perform audits/inspections, including source data verification.

10.2 Data Collection

The origin of source data will be specified and agreed in the Origin of Source Data form (REC5-121) with the Investigator. The following data may be recorded directly in the eCRF that will then be considered as source data:

- Date of birth and sex
- Vital signs, temperature, weight

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements:

- Investigation code
- Subject number
- That informed consent for participating in the study was obtained
- Diagnosis
- Investigation visit
- All AEs/ADEs/DDs

Relevant datapoints of TTE measurements will be entered in eCRF. TTE data will be collected and stored in DVDs.

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. The eCRFs will be completed, verified, monitored, and in the end of the study they will be signed by the Principal Investigator when all data are clean and without queries.

10.3 Access to Source Data and Documentation

The Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory authorities, and the Ethics Committee (EC), if required.

10.4 Database Management and Quality Control

Data management and handling will be conducted according to the investigation specific Data Management Plan in accordance with applicable guidelines and [redacted] SOPs ([redacted]).

The Investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. This includes maintaining any source documentation related to the investigation, including ECHO readings. The site will maintain a list of the subjects´ names and the Subject ID assigned to each individual participant Documents that identify the subject beyond the Subject ID will not be submitted to the sponsor (e.g. the signed informed consent document) and must be maintained in strict confidence by the Investigator, except to the extent necessary to allow inspections by the regulatory authorities and audits by the study monitor or sponsor representatives.

All data will be collected in the Electronic Data Capture (EDC) system by IBM Clinical Development. The specifics of the database design, testing, access and processes for data management and handling will be further defined in the investigation specific DMP and conducted in accordance with applicable guidelines and [redacted] SOP[redacted].

The Investigator must promptly review the completed eCRFs for each subject. As the person ultimately responsible for the accuracy of all eCRF data, the Principal Investigator must confirm the entries with his signature in each subject's eCRF.

After data review by the monitor, queries for any missing, out of range or questionable data will be generated for Investigator to answer and complete. The Investigator will answer the query as documented on the side of the eCRF. All queries must be answered.

10.5 Data Retention and Retention Period

10.5.1 Investigator Records Retention

All study documents must be retained by the Investigator for a period of at least 15 years after completion of the study. The Investigator must maintain adequate records of the clinical study, including:

- Completed eCRFs
- Medical records
- Signed informed consent forms
- ECG charts
- ECHO reports
- All correspondence between the Investigator and the EC, regulatory authorities, the sponsor, the CRO
- Any other pertinent data relevant to the study

The Investigator must not destroy any study specific documentation before receiving written permission for this from the sponsor.

10.5.2 Sponsor Records Retention

The sponsor will maintain the following records for at least 25 years after the last device has been manufactured or until the company ceases to exist:

- All correspondence pertaining to the investigation
- Signed and dated Investigator Agreements and signed and dated Investigator curriculum vitae that were current at the time of the study
- Copies of all EC approval letters, the EC review and approval procedures, and relevant EC correspondence
- Name and address of the institution where the clinical investigation was conducted, as well as records of approval from site administration

- Correspondence with authority as required by national legislation
- Insurance certificates
- Names/contact address of the monitor
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- Study training records for site personnel and sponsor/CRO personnel.

10.6 Quality Assurance

To assure accurate, complete and reliable data, the sponsor or its representatives will do the following:

- Provide instructional material to the investigational sites as appropriate
- Organize a meeting to instruct the Investigator and the study coordinator. This session will give instruction on the CIP, the IB, the completion of the eCRF and study procedures
- Perform monitoring visits at the investigational site
- Be available for consultation and stay in contact with study site personnel by email or phone
- Review and evaluate eCRF data

In addition, the sponsor or its representatives may check a sample of subject data recorded against source documents at the study site.

To ensure the safety of study participants, and to ensure accurate, complete, and reliable data, the Investigator will keep records of clinical notes and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the sponsor, the applicable regulatory authority, and the applicable EC with direct access to original source documents.

The study may be audited by the sponsor or its representatives at any time. Such an audit will be conducted according to a specific audit plan. Investigators will be given notice before an audit occurs.

The regulatory authorities may inspect the study site. The Investigator is responsible for notifying the sponsor of such an inspection immediately upon gaining knowledge of it. During the audit or inspection, the Investigator/institution will permit the auditor, EC reviewer, and regulatory inspector(s) direct access to all relevant medical records and other source data, study-related files and eCRFs.

11. ADMINSTRATIVE PROCEDURES AND RESPONSIBILITIES

11.1 Informed Consent

Prior to enrollment to the clinical investigation, ICF will be given to each prospective subject, including an explanation of the investigation, duration, explanation of medical record access and patient anonymity, and specifies that data will be recorded, collected, processed and may be transferred (to either EEA countries and/or non-EEA countries). The ICF may be utilized if approved by the responsible EC. Adequate time will be allowed for the subject to consider participation in the clinical investigation. Any coercion or undue influence of potential subjects to participate must be avoided, and the subject's legal rights should not be waived. The subject will also be informed of his/her right to withdraw from the study at any time without giving a reason. If the subject is willing to participate in the investigation, both the subject and the Investigator or designated sub-Investigator who conducted the informed consent process must sign and date the ICF in accordance with local national requirements. The original signed ICF will be filed in the Investigator Site Files (ISF). The subject then will be given a copy of the signed ICF.

The ICF must be fully signed and dated prior to data collection or any other investigation-related activities required by the CIP. Failure to obtain signed informed consent renders the patient ineligible for the investigation

The ICF complies with the ISO 14155:2011 standard and is considered appropriate for this study will be submitted to the EC. The ICF will be in Finnish and will contain language that is non-technical and understandable to the subject. Any changes to the ICF suggested by the Investigator must be agreed by Medtentia International Ltd Oy before submission to the EC and a copy of the EC approved version must be provided to the CRA after EC approval.

11.2 Statement of Compliance

This clinical investigation was designed and shall be implemented and reported in accordance with the international standard of ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice, and with the ethical principles laid down in the Declaration of Helsinki (WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects).

This clinical investigation will be conducted in compliance with regional or national regulations, as appropriate.

11.3 Approval from Ethics Committee or Regulatory Authority

The clinical investigation will not begin until the approval from both EC and regulatory authority has been obtained, as appropriate.

The CIP and the final version of the ICF must be approved or given a favorable opinion in writing by a properly constituted EC before investigation start. A signed and dated statement from the EC that the CIP and ICF have been approved must be forwarded to Medtentia International Ltd Oy before study initiation.

The study must be reviewed and approved by the responsible regulatory authority before study initiation, according to local and national regulations. Any additional requirements imposed by the EC or regulatory authority will be followed.

If any alterations, other than changes of an administrative nature only, are made to the study CIP, a formal CIP amendment will be issued and submitted to the relevant EC for approval. The amendment will not be implemented until EC approval.

Since this is short clinical investigation, no amendments are expected.

11.4 Subject Data Protection

The ICF explains that the data will be stored in a database, maintaining confidentiality in accordance with national data legislation, and that only authorized representatives of the Sponsor, regulatory authority or an EC may require direct access. The computerized data will be identified by subject number only. The Investigator will file the medical records relevant to the investigation, including medical history, for verification of data.

Identification list, which includes enough information to link records, i.e. eCRF and clinical records will be preserved for possible future inspections/audits and will be available only for monitoring and auditing purposes.

Information collected during the study will be stored in Investigator Site Files (ISF) at the site. Clinical Investigation Master Files (CIMF) will be kept at [redacted] office until the end of the study, after which the CIMF will be shipped to the sponsor.

11.5 Investigator Responsibilities for EC and Regulatory Authority

Prior to study start, the Investigator is required to sign a Clinical Investigation Plan signature page confirming his agreement to conduct the study in accordance with all of the instructions and procedures found in this CIP and associated documents and to give access to all relevant data and records to Medtentia International Ltd Oy, monitors, auditors, Quality Assurance

representatives, designees, EC and regulatory authorities as required. If an inspection of the investigational site is requested by a regulatory authority, the Investigator must immediately inform Medtentia International Ltd Oy that this request has been made.

11.6 Imposed Additional Requirements

This section is not applicable.

11.7 Reporting Responsibilities

11.7.1 Investigator Reporting Responsibilities

The Investigator or designee is responsible for completing (including review and signature) eCRFs, as well as for submitting reports to the sponsor of deviations from the CIP. If any action is taken by the EC with respect to the investigation, the Investigator will forward the information to the sponsor as soon as possible.

11.7.2 Sponsor Reporting Responsibilities

The sponsor is responsible for preparation and reporting the final clinical investigation report according to the guideline presented in Annex C of ISO 14155-1:2011. This report, or parts of it, must be submitted to the relevant authorities, if applicable.

11.8 Insurance

The sponsor maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, proof of the clinical trial insurance policy will be provided to the EC. If required by national regulations, indemnification will be provided.

11.9 Amendments to the Clinical Investigation Plan

Since this is short clinical investigation, no amendments are expected.

11.10 Deviations from the Clinical Investigation Plan

The Investigator is not allowed to deviate from the CIP, except when necessary to protect the subject's life, physical well-being or right in an emergency or when caused by unforeseen circumstances that are beyond the Investigator's control (e.g. subject did not attend scheduled visit). Prior approval by the sponsor is required for changes in or deviations from the CIP,

except in an emergency. If the changes or deviations may affect the rights, safety, or welfare of participants, EC approval is required. Such approval will be documented in writing and maintained in the ISF and Trial Master File (TMF).

The site will report all deviations, regardless of whether medically justifiable or taken to protect the subject in an emergency, to the sponsor in a timely manner on a protocol deviation form. In addition, the Investigator is required to adhere to the EC procedures for reporting deviations.

Deviations include, but are not limited to the following list:

- Failure to obtain informed consent prior to conducting study specific activities
- Incorrect version of the ICF used
- CIP-required testing and/or measurements were not done or were done incorrectly
- Source data permanently lost.

A sponsor representative or monitor will review site compliance with regard to deviations at the monitoring visit. The monitor will discuss any deviations that occurred at the investigational site directly with the Investigator and will summarize the findings in a follow-up letter to the site. In addition, all deviations from the CIP will be documented in the final study report.

11.11 Corrective and Preventive Action and Principal Investigator Disqualification Criteria

See section 11.10 Deviations from the CIP. After analyzing and taking corrective actions, site personnel will be retrained by the sponsor or its representatives on the relevant study procedures. All necessary measurements will be taken to prevent reoccurrence of the CIP deviation.

11.12 Suspension or Premature Termination

This section is not applicable.

11.13 Investigator and Site Selection

Investigator and Site are pre-selected by Medtentia International Ltd Oy. The Principal Investigator will be cardiologist [redacted] and the site [redacted].

12. PUBLICATION POLICY

All information supplied by the sponsor in connection with this investigation will remain the sole property of the sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the sponsor and will not be used except in the performance of this investigation.

The publication of study results will be agreed between the sponsor and the Investigator. The sponsor intends to publish the results of the study. However, the sponsor retains the right to review and approve in writing any publication, poster, presentation or manuscript before they are made public in order to prevent publication of any confidential information.

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14. APPENDICES

14.1 New York Heart Association Functional Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: (New York Heart Association Functional Classification, 2013) American Heart Association https://manual.jointcommission.org/releases/TJC2018A/DataElem0439.html

Accessed 28 Mar 2019.