Medtronic

Clinical Investigation Plan

Study Title	PRESERVE - MITRAL **P**rospective **RE**gistry to **S**tudy Clinical Outcom**E**s of **R**epair of Mitral **V**alv**E**s in South Asia.
Clinical Investigation Plan Identifier	MDT16016SUR002
Study Product Name	Profile 3D™, CG Future® annuloplasty systems
Sponsor/Local Sponsor	Medtronic plc. Clinical Research Mailstop: MVS66 Mounds View South 8200 Coral Sea St. NE Mounds View, MN 55112 **Regional Sponsor:** Vinay Rajan, Ph.D India- Medtronic Pvt. Ltd. Solitaire Corporate Park, Bldg No. 12, 4th Floor, Andheri -Ghatkopar Link Road, Andheri-East Mumbai, Maharashtra 400 093 INDIA Contact Number: +91-22-33074700
Document Version	1.0 / 10-APR-2017

Confidentiality Statement

Study Sponsor Contact Information

Medtronic contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the centers as needed.

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1. Investigator Statement

Study product Name	Profile 3D™, CG Future®
Sponsor	Medtronic plc Clinical Research Mailstop: MVS66 Mounds View South 8200 Coral Sea St. NE Mounds View, MN 55112 **Regional Sponsor:** Vinay Rajan, Ph.D India- Medtronic Pvt. Ltd. Solitaire Corporate Park, Bldg No. 12, 4th Floor, Andheri -Ghatkopar Link Road, Andheri-East Mumbai, Maharashtra 400 093 INDIA
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I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the India Good Clinical Practice (India GCP). I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AC	Advisory Committee
ASADE	Anticipated Serious Adverse Device Effect
CDSCO	Central Drugs Standard Control Organization
CIP	Clinical Investigation Plan
CMP	Clinical Management Plan
CRS	Clinical Research Specialist
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
CVD	Cardiovascular Disease
DCGI	Drug Controller General of India
DD	Device Deficiency
DMC	Data Monitoring Committee
DRF	Data Release Form
DTL	Delegated Task List
EC	Ethics Committee
ECG	Electrocardiogram/Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FU	Follow Up
GCP	Good Clinical Practice

Term	Definition
HF	Heart Failure
IRB	Institutional Review Board
LAD	Left Atrial Diameter
LVEDD	Left Ventricular End Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVOTO	Left Ventricular Outflow Tract Obstruction
MACCE	Major Adverse Cardiac & Cerebrovascular Event
MI	Myocardial Infarction
MR	Mitral Regurgitation
MS	Mitral Stenosis
MV	Mitral Valve
NYHA	New York Heart Association
PI	Principal Investigator (one per site)
PIC	Patient Informed Consent
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAM	Systolic Anterior Motion
SOP	Standard Operating Procedure
TEE	Transoesophageal Echocardiograph
TTE	Transthoracic Echocardiograph
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

3. Synopsis

Title	PRESERVE - MITRAL **P**rospective **RE**gistry to **S**tudy Clinical Outcom**E**s of **R**epair of Mitral **V**alv**E**s in South Asia.
Clinical Study Type	Post Market Registry
Product Name	Profile 3D™, CG Future®
Sponsor	Medtronic plc. Clinical Research Mailstop: MVS66 Mounds View South 8200 Coral Sea St. NE Mounds View, MN 55112
Regional Sponsor	Vinay Rajan, Ph.D India- Medtronic Pvt. Ltd. Solitaire Corporate Park, Bldg No. 12, 4th Floor, Andheri -Ghatkopar Link Road, Andheri-East Mumbai, Maharashtra 400 093 INDIA
Indication under investigation	Patients suffering from mitral valve disease and indicated for a mitral valve repair procedure with Profile 3D™ and CG Future® annuloplasty system as part of standard of care, in accordance with the product label indications (instructions for use), contraindications, and warnings
Investigation Purpose	There is limited local evidence on mitral repair products in South Asia and a prospective post market registry will provide real world data on clinical outcomes
Product Status	Profile 3D™ and CG Future® annuloplasty systems are indicated for the reconstruction and/or remodeling of the pathological mitral valve. The devices are approved and commercially available in India and are commercially available in Bangladesh and Nepal.
Primary Objective(s)	The objective of this registry is to gather data on the clinical outcomes of Medtronic mitral repair products (Profile 3D™ and CG Future® annuloplasty systems) in the approved intended use up to 12 months from the day of procedure
Secondary Objective(s)	Characterize the demographics of the patients undergoing mitral valve repair using annuloplasty systems in India, and assess the functional

	and procedural outcomes of the procedure.
Study Design	PRESERVE-Mitral Registry is a prospective non-randomized, non-interventional, post-market registry.
Sample Size	200
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Patients with valvular insufficiency and/or stenosis and indicated for the reconstruction and/or remodeling of pathological mitral valves with Profile 3D™ and CG Future® annuloplasty systems 2. Indications and contraindications provided in the product Instructions for Use 3. Subject is 18 years of age or older 4. The patient or his/her Legally Authorized Representative (LAR) has been informed about the nature of the registry and the patient informed consent for study participation has been obtained prior to performing any study-related procedures from the subject or Legally Authorized Representative, as per applicable local requirements Exclusion Criteria: 1. Contraindications as per IFU: a. Heavily calcified valves b. Valvular retraction with severely reduced mobility c. Active bacterial endocarditis 2. Aortic valve replacement as concomitant procedure 3. Already participating in another clinical study, possibly leading to bias and jeopardizing the scientific appropriate assessment of the study endpoints
Study Procedures and Assessments	• Baseline/Pre-Operative (data from most recent assessment before planned implant date preferred, not exceeding 60 days) • Implant • Discharge (date of discharge or 7 days post procedure, whichever comes first) • 3 to 6 months (data reported from 90 days up to 210 days post procedure, whichever comes later) • 12 months (data reported up to day 395 (365 +/- 30 days) post procedure date will be collected)
Safety Assessments	All relevant safety data will be collected and reported per local regulations and EC/IRB requirements

4. Introduction

4.1. Background

Cardiovascular diseases are the leading cause of mortality in India, contributing to 25% of all mortality in the country. The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 100,000 population in India is higher than the global average of 235 per 100,000 population [1].

Mitral valve regurgitation

One of the important pathologies seen in patients with cardiovascular disease is mitral valve regurgitation and insufficiency. Patients might suffer from different types of mitral valve dysfunction leading to different levels of regurgitation. The following classification of dysfunctioning valves was introduced by Carpentier [2]:

- Type I: the free edges of the leaflets remain below the plane of the annulus during systole and open normally during diastole;
- Type II: the free edge of one or both leaflets overrides the plane of the annulus during systole;
- Type III: one or both leaflets do not open fully during diastole or close fully during systole
  - IIIa: restricted leaflet motion during systole and diastole
  - IIIb: restricted leaflet closure during systole

Type I dysfunction is the result of annular dilatation, often caused by myocardial infarction (MI). In most cases, type II dysfunction is a result from rupture or elongation of either the papillary muscles or the chordae tendinae, possibly as a result of MI. Type IIIa is mostly caused by leaflet thickening/retraction, chordal thickening/shortening/fusion or commissural fusion. Type IIIb dysfunction is the most common form of ischemic mitral regurgitation (IMR) [3].

Apart from the types of valve dysfunction, the severity of regurgitation can be gauged as per ASE guidelines [4] (see Table 1).

Table 1: ASE Guidelines for MR Severity Grading with Echocardiography [4]

	MR Severity*			
	Mild	Moderate		Severe
Structural				
MV Morphology	**None or mild leaflet abnormality** (e.g., mild thickening, calcifications or prolapse, mild tenting)	Moderate leaflet abnormality or moderate tenting		**Severe valve lesions** (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation)
LV and LA size†	Usually normal	Normal or mild dilated		Dilated‡
Qualitative Doppler				
Color flow jet area§	**Small, central, narrow, often brief**	Variable		Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence‖	**Not visible, transient or small**	Intermediate in size and duration		**Large throughout systole**
CWD jet	Faint/partial/parabolic	Dense but partial or parabolic		Holosystolic/dense/**triangular**
Semiquantitative				
VCW (cm)	<0.3	Intermediate		≥0.7 (>0.8 for biplane)¶
Pulmonary vein flow#	**Systolic dominance** (may be blunted in LV dysfunction or AF)	Normal or systolic blunting#		Minimal to no systolic flow/**systolic flow reversal**
Mitral inflow**	**A-wave dominant**	Variable		E-wave dominant (>1.2 m/sec)
Quantitative††,‡‡				
EROA, 2D PISA (cm^2)	<0.20	0.20-0.29	0.30-0.39	≥0.40 (may be lower in secondary MR with elliptical ROA)
RVol (mL)	<30	30-44	45-59††	≥60 (may be lower in low flow conditions)
RF (%)	<30	30-39	40-49	≥50

ROA, Regurgitant orifice area.
Bolded qualitative and semiquantitative signs are considered specific for their MR grade.
*All parameters have limitations, and an integrated approach must be used that weighs the strength of each echocardiographic measurement. All signs and measures should be interpreted in an individualized manner that accounts for body size, sex, and all other patient characteristics.
†This pertains mostly to patients with primary MR.
‡LV and LA can be within the "normal" range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR.
§With Nyquist limit 50-70 cm/sec.
||Small flow convergence is usually <0.3 cm, and large is $ 1 cm at a Nyquist limit of 30-40 cm/sec.
¶For average between apical two- and four-chamber views.
#Influenced by many other factors (LV diastolic function, atrial fibrillation, LA pressure).
**Most valid in patients >50 years old and is influenced by other causes of elevated LA pressure.
††Discrepancies among EROA, RF, and RVol may arise in the setting of low or high flow states.
‡‡Quantitative parameters can help subclassify the moderate regurgitation group.

Mitral valve repair – global perspective

Mitral valve repair is established as a procedure to alleviate mitral valvular insufficiency/stenosis. The pathophysiology of mitral valve insufficiency can be ischemic, rheumatic, degenerative, congenital, infective, myxomatous, etc.

Mitral valve repair may lead to better outcomes as compared to replacement. The overall survival of patients undergoing valve repair was found to be significantly superior to that of patients undergoing valve replacement, with 5- and 10-year survival rates, respectively, of 83±3% and 68±6% (repair, n=195) and 69±3% and 52±4% (replacement, n=214) [5].

Western studies on mitral valve repair have typically focused on patients with ischemic pathophysiology. In a study of patients with chronic moderately severe to severe mitral regurgitation (grade 3-4) and ischemic or dilated cardiomyopathy, all 121 patients underwent mitral valve repair (8 with a flexible ring; 113 with a semi-rigid ring) with concomitant surgery. The 30-day mortality was 3.3% and survival rates at 3 and 30 months were 95% and 91% respectively. At discharge, all 117 patients had MR level of 2 or less. No difference was found between patients implanted with flexible and semi-rigid annuloplasty rings [6].

One group of researchers investigated leaflet curvature and stress distribution of the mitral valve using numerical and experimental data and found that "it seems reasonable to hypothesize that a saddle-shaped annuloplasty ring may increase mitral valve repair durability by reducing leaflet and chordal strain". The shape of Medtronic's Profile 3D ring exactly matches the shape described by the authors [7].

Guidelines

Current ACC/AHA guidelines [8] state that mitral valve repair is recommended in preference to mitral valve replacement in certain patients with chronic severe primary MR limited to posterior leaflet, or involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished. Concomitant repair is indicated for patients with chronic severe primary MR if they undergo cardiac surgery.

Mitral valve repair is considered reasonable in asymptomatic patients with chronic severe primary MR with preserved LV function, and reasonable as a concomitant procedure in patients with chronic moderate primary MR when undergoing cardiac surgery for other indications. Mitral valve surgery (including either repair, commissurotomy or replacement) may be considered in patients with rheumatic mitral valve disease when surgical treatment is indicated.

The guidelines also state that mitral valve surgery is indicated for severely symptomatic patients with severe mitral stenosis who are not at risk for surgery and who are not candidates for or have failed previous percutaneous mitral balloon commissurotomy.

Regional perspective

Despite the guidelines, there may be local and regional differences in the standard practice in different geographies. While there are some Indian studies that have looked into mitral valve repair [9], [10], [11], there is still a need to gather more local evidence on clinical outcomes at long term follow up (12 months).

Table 2: Indian studies on mitral valve repair procedures

	Gupta, et al (2010) [9]	Choudhary, et al (2001) [10]	Saravana, et al (2015) [11]
Sample Size	n = 44	n = 818	n = 163
Prospective/Retrospective	Prospective	Retrospective	Prospective
Disease type	100% rheumatic	88% rheumatic 6% congenital 4% myxomatous 1% infective 1% ischemic	43% rheumatic 25% degenerative 21% ischemic 9% congenital 1% subacute bacterial endocarditis 1% other
Lesion type	45% pure MR 39% MR+MS 16% pure MS	53% pure MR 47% MR+MS	94% >=grade 3 MR 6% MR+MS
NYHA class	91% NYHA III/IV	64% NYHA III/IV 14% with congestive HF	88% NYHA III/IV

The significant proportion of mitral valve repair patients in India have rheumatic disease. Mitral valve repair is more technically challenging in this population, and is associated with higher failure rate. [10].

It is estimated that rheumatic heart disease prevalence is in the range of 1.5 to 2 per 1000 individuals (2–2.5 million cases in absolute numbers) in India, with an estimated 88,674 deaths (7 per 100,000 population) in the year 2010 [1].

The Global Rheumatic Heart Disease Registry (REMEDY study) enrolled patients presenting with rheumatic disease in 12 African countries, Yemen and India [12]. The patients with rheumatic heart disease were young (median age 28 years) and largely female (66.2%). The majority (63.9%) had multivalvular disease complicated by congestive heart failure. The majority of cases of mitral stenosis (72.9%) and mitral regurgitation (60.4%) had moderate-to-severe disease. A stark finding was that the utilization of valve surgery and valvuloplasty in patients with rheumatic heart disease in low-middle-income countries like India was 27.8%. Amongst the patients having native rheumatic valve disease with no percutaneous or surgical interventions, it was found that children in the first decade of life presented mostly with pure mitral regurgitation, and in the second decade of life, presented with mixed mitral and aortic valve disease with dominant mitral lesion [12].

Given this background, it is clear that the significant body of evidence for mitral valve annuloplasty from the west may not give a realistic picture of patients undergoing the same procedure in South Asia. Due to the difference in disease pathophysiology, the significant population of patients with rheumatic disease and differing surgical practice, there is a need to conduct a geography-specific study to understand the clinical outcome of patients undergoing mitral valve annuloplasty in the region. PRESERVE-Mitral, a

prospective registry to study long term performance of annuloplasty systems is thus proposed to document clinical outcomes, physician practice and report on outcomes in these patients.

4.2. Purpose

There is limited local evidence on mitral repair products in South Asia and a prospective post-market registry will provide real world data on clinical outcomes.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The objective of this registry is to gather data on the clinical outcomes of Medtronic mitral repair products (Profile 3D™ and CG Future® annuloplasty systems) in the approved intended use up to 12 months from the day of procedure.

5.1.2. Secondary Objective(s)

Characterize the demographics of the patients undergoing mitral valve repair using annuloplasty systems in South Asia, and assess the functional and procedural outcomes of the procedure.

5.2. Endpoints

5.2.1. Primary Endpoint

To evaluate clinical outcomes at 12 months post procedure:

1. Improvement in MR (grade)

   This will be determined by assessing the level of mitral valve regurgitation using echo, in subjects at 12 months post procedure compared to the level at baseline. The levels of regurgitation, level 0-4, will correspond to the ASE guidelines ranging from no MR, Mild MR, Moderate MR, Moderate-to-Severe MR and Severe MR, as described in Table 1 above.

2. All cause mortality

   All deaths occurring from any cause post procedure.

5.2.2. Secondary Endpoint(s)

- Characterization of patient demographics and pathophysiology of mitral valve disease

  The patients will be identified by collecting the following patient characteristics at baseline: age (in years), gender, previous cardiovascular surgery, symptoms of heart failure, cardiac rhythm,

New York Heart Association (NYHA) classification, risk factors, level of regurgitation, type of mitral valve deficiency, etc.

- Improvement in MR grade at discharge and first follow up (3-6 months)

  This will be determined by assessing the level of mitral valve regurgitation using echo, in subjects at discharge and 3-6 months post procedure compared to the level at baseline. The levels of regurgitation, level 0-4, will correspond to the ASE guidelines ranging from no MR, Mild MR, Moderate MR, Moderate-to-Severe MR and Severe MR, as described in Table 1 above.

- Improvement in NYHA functional class at discharge, first follow up (3-6 months) and second follow up (12 months) compared to baseline

  The New York Heart Association (NYHA) Functional Classification is a system for defining cardiac disease and related functional limitations into four broad categorizations as defined in Table 3 below.

Table 3: NYHA functional class definitions

Classification	Description
Class I	Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

- Hospitalization for Heart Failure at 6 months and at 12 months post procedure

  Hospitalizations for Heart Failure are defined as a non-elective hospital admission for signs and symptoms related to heart failure that results in a one-night stay (i.e., where the admission date and the discharge date differ by at least one calendar day). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. The occurrence of hospitalization for heart failure will be evaluated at 6 months and 12 months post procedure.

- Mitral valve re-intervention at discharge, 6 months and at 12 months post procedure

  Following the completion of the procedure, defined as the subject leaving the operating theater with an implanted Profile 3D™ or CG Future® annuloplasty system, any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces the previously implanted annuloplasty system will be termed re-intervention. In addition to surgical

reoperations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered re-interventions. The re-intervention rate will be evaluated at discharge, 6 months and 12 months post procedure.

- Stroke at 6 months and at 12 months post procedure

  Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours. The occurrence of stroke will be evaluated at 6 months and 12 months post procedure.

- New onset of Atrial Fibrillation, as evaluated through follow up ECG at discharge, first follow up (3-6 months) and at second follow up (12 months)

  New onset of AF is defined as when the subject did not present with prior history of AF at baseline nor was AF detected at baseline visit, but AF did manifest post procedure and was either diagnosed during the study visits (discharge, 3-6 months or 12 months visit) or was otherwise diagnosed during the duration of subject participation in the study. The incidence of new onset AF will be evaluated at discharge, first follow up (3-6 months) and at second follow up (12 months).

- Number of attempts required for procedural success, and bypass time as a measure of procedural complexity, as measured by standard operating room procedures at the site.

6. Study Design

PRESERVE-Mitral is a prospective non-randomized non-interventional post-market registry. A total of 200 patients who are eligible and who are intended to be implanted with a Profile 3D™ or CG Future® Annuloplasty system in the surgical repair procedure will be included in the study.

The subjects will be evaluated at discharge for evaluation of procedural success and subsequently followed up as per standard-of-care at the site from 3-6 months (90 days to 210 days) post procedure and at 12 months (365 days +/- 30 days) post procedure for assessment of longer term outcome at which time subjects will also exit the study. Echo images will be evaluated pre-implant, intra-op, discharge and during follow ups, according to the standard routine in the center.

Patients eligible for mitral valve repair and compliant with the enrollment criteria will be considered by the investigator for inclusion in the study.

6.1. Duration

The enrollment period is anticipated to take about 20 months. The study is expected to start enrolling in July 2017. With a maximum follow-up period of 12 months, the study is expected to last 32 months after the first patient enrollment. It is expected that an additional 4 months would be required for data analysis, and preparation of the publication. This study will be conducted in 10 centers in India, Nepal

and Bangladesh. Each center can include a maximum of 40 subjects in the study, which is 20% of the overall enrollment for the study. There is no minimum enrollment per site applicable for this study.

A site may be selected for participation in the registry if the site complies with the following requirements:

- Sites are expected to adhere to Indian GCP and other local regulations as applicable.
- The site will appoint a Principal Investigator at the physician-in-charge level or above with appropriate experience and qualifications to oversee investigational procedures.
- The PI and other investigators have knowledge and experience in mitral valve repair, e.g. implanting the Profile 3D or CG Future Annuloplasty systems.
- The site has the necessary facilities to conduct the registry (for example echocardiography).
- The site applies a 3-6 month and 12 month follow up as standard practice of care for these patients.
- Site is willing to comply with all requirements of the regulatory agency, Ethics Committees, or Institutional Review Boards, and the CIP.

6.2. Rationale

This study is a post-market registry, studying products that are already in the markets being studied. The study is designed to be observational, following the standard of care at each centre, in order to obtain real world data on the use of the products. The time period of the first follow up is kept flexible, in accordance with the variation in practice at different centres and in order to maximize compliance. The second follow up (12 month) is a standard timepoint for evaluation of longer term outcomes at all centres. All data collected in the study are as per the centre's standard practice, and no interventional procedure will be added in the study.

7. Product Description

7.1. General

The Medtronic Profile 3D™ Annuloplasty Ring (Figure 1), Model 680R, consists of a titanium core overmolded with silicone and covered with polyester fabric. The ring must be implanted in the mitral position. The ring is marked at three points by colored sutures; two markers correspond to the trigons of the mitral valve, and one identifies the midpoint of the device. The device size is identified by the inside diameter of the ring at its widest point. The titanium core enables radiographic visualization of the device. Non-clinical testing has demonstrated that the Profile 3D™ Ring is compatible with Magnetic Resonance Imaging (MRI) under normal Magnetic Resonance mode (additional information is provided in Appendix L.1.

Figure 1: Profile 3D™ Annuloplasty Ring

The indications for use are to reconstruct and/or remodel the pathological mitral valve. Valvular insufficiency and/or stenosis may be corrected by appropriate repair and annular remodeling. The Profile 3D product is contraindicated for use with highly calcified valves or in retracted valves with severely reduced leaflet mobility. It is also contraindicated for patients suffering from active bacterial endocarditis.

The Medtronic Profile 3D™ Annuloplasty Ring is commercially released (CE-mark since 2008) and in this study, the Profile 3D ring will be applied only within the indications for use. At the time the protocol was finalized, the Medtronic Profile 3D™ Annuloplasty Ring was also approved in the additional geographies (Nepal) in which the study will be conducted. The technical aspects for the Profile 3D Annuloplasty Ring – Model 680R – are provided in Appendix L.1.

The Medtronic Accessories, 768S Profile 3D™ Sizer Set including 9 Profile 3D™ sizers 24-40 mm, are used to identify the size of the ring. In addition, the Annuloplasty Handle Accessories (7686 Annuloplasty Handle (216 mm length) and/or 7686XL Annuloplasty Handle (373 mm length)) are used to be able to implant the profile ring. The T76880 Profile 3D™ Accessory Tray serves to organize and store the various accessories when not in use and may be used to hold the accessories during sterilization. All accessories are also commercially available in the countries/geographies in which the study will take place.

Figure 2: The Medtronic CG Future® Annuloplasty System (Ring and Band)

The Medtronic CG Future® Annuloplasty Ring Model 638R and the Medtronic CG Future® Annuloplasty Band Model 638B (hereafter referred to as CG Future® Annuloplasty Ring/Band) for mitral valve repair are designed to predictably remodel the annulus to maintain apposition of the anterior and posterior leaflets. Correct annuloplasty ring/band sizing is an important element to achieve a successful repair.

The CG Future® COMPOSITE Ring is the first composite ring to offer posterior remodeling while maintaining anterior flexibility. A flexible anterior segment seamlessly connects to the ring's semi-rigid posterior, providing the support needed to dynamically remodel the annulus, thereby allowing physiologic movement throughout the cardiac cycle. It has an unique eyelet design for easy anchoring to the trigones. Semi-rigid design offers enough flexibility to allow movement of the mitral annulus during the cardiac cycle. The band is ideal for small incisions and minimally invasive procedures where visibility and access to the anterior portion of the mitral annulus may be limited.

The CG Future® Ring is available in eight sizes ranging from 24 mm to 38 mm.

The CG Future® Band is available in seven sizes ranging from 26 mm to 38 mm.

7.2. Manufacturer

The products are manufactured by Medtronic, PLC.

7.3. Packaging

The PROFILE 3D™ and CG Future® annuloplasty systems are commercially available. Refer to IFU for packaging and storage information.

7.4. Intended Population

The PROFILE 3D™ and CG Future® systems are indicated for the reconstruction and/or remodeling of pathological mitral valves. Valvular insufficiency and/or stenosis may be corrected by appropriate repair and annular remodeling.

CONTRAINDICATIONS

- Heavily calcified valves.
- Valvular retraction with severely reduced mobility.
- Active bacterial endocarditis.

7.5. Equipment

All equipment for collecting data will be as available at the site.

7.6. Product Use

The product should be used as per the Directions For Use outlined in the Instructions For Use insert that comes packaged with the products (Appendix L.1.).

7.7. Product Training Requirements

This is a post-market registry, hence there is no requirement for specific product training.

7.8. Product Receipt and Tracking

All devices being used in this study are commercially available in the countries/geographies in which the study will be conducted. Therefore, the devices will be used off the shelf. The products are provided to the hospital with the appropriate language labeling. In this study, the Profile 3D and CG Future products will be applied only within the indications for use. Existing procedures for commercial product regarding distribution, shipment, receipt and tracking of these devices will be followed. Additional device traceability is not applicable for this study.

7.9. Product Storage

All devices being used in this study are commercially available in the selected countries/geographies in which this study will take place.

Refer to the Instructions for Use for storage of the study device (Appendix L.1.).

7.10. Product Return

The study will follow the commercial process for explanted device to be properly retrieved, packaged and shipped to sponsor, which is the same as the process followed for the device in the market.

7.11. Product Accountability

Except documentation of serial numbers and model numbers of devices being used in this study, there are no device tracking requirements. The documentation of these numbers needs to be recorded on the eCRF.

8. Selection of Subjects

8.1. Study Population

The patient population includes all patients suffering from mitral valve disease, indicated for a mitral valve repair procedure, either as a stand-alone procedure or concomitant to another procedure (for example, coronary artery bypass grafting, tricuspid valve repair, treatment of atrial fibrillation, etc. but excluding patients undergoing aortic valve replacement) and for which the surgeon considers the implantation of a Profile 3D™ or CG Future® annuloplasty system most appropriate to reconstruct the regurgitant valve.

8.2. Subject Enrollment

A subject is considered enrolled in this study at the time at which he/she signed the Patient Informed Consent Form.

The investigator will maintain a log of all subjects enrolled in the study assigning an identification code linked to their names, alternative subject identification or contact information.

8.3. Inclusion Criteria

1. Patients with valvular insufficiency and/or stenosis and indicated for the reconstruction and/or remodeling of pathological mitral valves with Profile 3D™ and CG Future™ annuloplasty systems
2. Indications and contraindications provided in the product Instructions for Use
3. Subject is 18 years of age or older
4. The patient or his/her Legally Authorized Representative (LAR) has been informed about the nature of the registry and the patient informed consent for study participation has been obtained prior to performing any study-related procedures from the subject or Legally Authorized Representative, as per applicable local requirements

8.4. Exclusion Criteria

1. Contraindications as per IFU:
   a. Heavily calcified valves
   b. Valvular retraction with severely reduced mobility
   c. Active bacterial endocarditis
2. Aortic valve replacement as concomitant procedure
3. Already participating in another clinical study, possibly leading to bias and jeopardizing the scientific appropriate assessment of the study endpoints

9. Study Procedures

9.1. Schedule of Events

The following table (Table 1) lists the schedule of events for the study for each study related visit.

Table 1: Schedule of Events

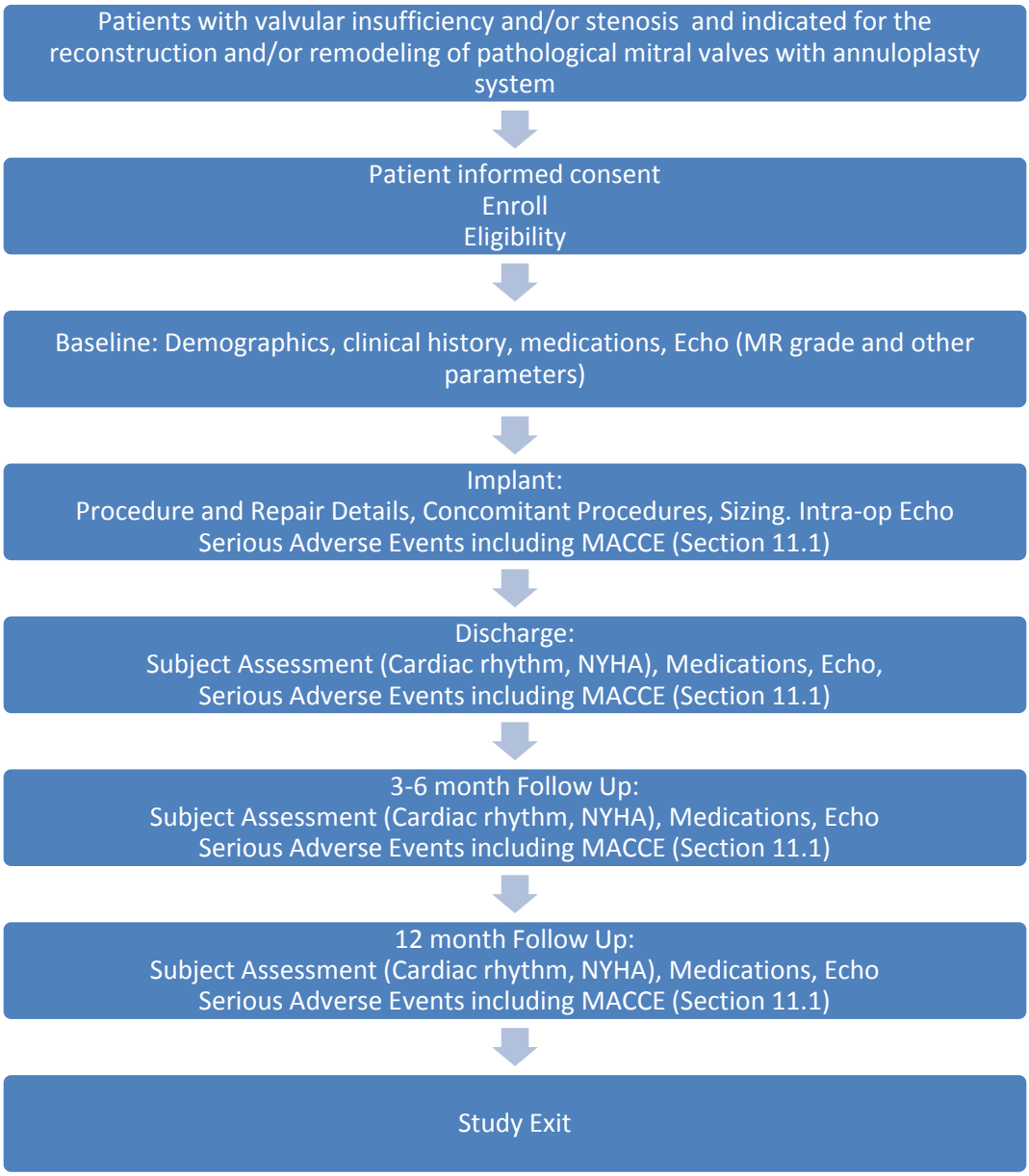
Visit	Procedure	Data Collection
Baseline/Pre-Operative (data from most recent assessment	Enrollment	Consent Eligibility assessment (inclusion/exclusion criteria)
	Patient Data	Patient Demographics

before planned implant date preferred, not exceeding 60 days)		Pre-Operative Clinical History (cardiac rhythm, previous procedures, symptoms, risk factors, lesion information, etc.) Medications
	Echo	MR Mitral Gradient Leaflet coaptation Aortic and Tricuspid valves HF parameters (LVEF, LVEDD, LAD, etc.)
Implant	Implant Data	Procedure Details Repair Details Concomitant Procedures Sizing Serious Adverse Events including major adverse cardiac or cerebrovascular events (MACCE) as defined in section 11.1
	Echo	Intra-op echo
Discharge (date of discharge or 7 days post procedure, whichever comes first)	Health Assessment	Subject Assessment (Cardiac rhythm, NYHA, etc.) Serious Adverse Events including major adverse cardiac or cerebrovascular events (MACCE) as defined in section 11.1 Medication
	Echo	MR Mitral Gradient Leaflet coaptation Aortic and Tricuspid valves HF parameters (LVEF, LVEDD, LAD, etc.)
3-6 Month Follow Up (data reported from 90 days up to 210 days post procedure, whichever comes later)	Health Assessment	Subject Assessment (Cardiac rhythm, NYHA, etc.) Serious Adverse Events including major adverse cardiac or cerebrovascular events (MACCE) as defined in section 11.1 Medication
	Echo	MR Mitral Gradient Leaflet coaptation

		Aortic and Tricuspid valves HF parameters (LVEF, LVEDD, LAD, etc.)
12 Month Follow Up (data reported up to day 395 (365 +/- 30 days) post procedure date will be collected)	Health Assessment	Subject Assessment (Cardiac rhythm, NYHA, etc.) Serious Adverse Events including major adverse cardiac or cerebrovascular events (MACCE) as defined in section 11.1 Medication
	Echo	MR Mitral Gradient Leaflet coaptation Aortic and Tricuspid valves HF parameters (LVEF, LVEDD, LAD, etc.)
	Study Exit	Exit

The following figure (Figure 3) is indicative of the study methods.

Figure 3: Study Methods



9.2. Subject Screening

Patients indicated for mitral repair procedure will be considered for enrollment in this study, and screened based on inclusion/exclusion criteria mentioned in Section 8. Site will maintain a Screening Log to maintain screening information.

9.3. Prior and Concomitant Medications

During the course of the study, subjects will continue to take medication as advised by their physician per standard of care. The study does not advise or limit the subject from any particular medication.

9.4. Subject Consent

The investigator or authorized designee must obtain written informed consent before any study related activity takes place.

Prior to the consent discussion, the patient should receive the EC/IRB approved Patient Information and Patient Informed Consent Form. During the consent discussion the investigator or his/her authorized designee must fully inform the patient of all aspects of the study that are relevant to the patient's decision to participate in the study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Information and the Patient Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the Patient Information and the Patient Informed Consent Form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the study, the Patient Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Patient Informed Consent Form was accurately explained and clearly understood by the patient, and that informed consent was freely given.

After all persons have signed and dated the Patient Informed Consent Form, the investigator must provide the patient with a copy of the Patient Information and the signed and dated Patient Informed Consent Form.

This study does not require any additional interventions other than the standard of care, and hence, the subject will be treated as per physician's discretion in case of requirement of emergency treatments.

It will be the investigator's responsibility to fulfil any additional EC requirements, if any on the informed consent process.

9.5. Randomization and Treatment Assignment

PRESERVE-Mitral is a prospective non-randomized non-interventional post-market registry and does not involve randomization.

9.6. Medication Compliance

The study will not be prescribing any particular medication, all subjects will continue on their medication as prescribed by their physicians per standard practice.

9.7. Assessment of Efficacy

This is a post-market registry assessing long term clinical outcomes.

9.8. Assessment of Safety

Serious Adverse Events and Device Deficiencies throughout the study will be collected and recorded in the AE and DD CRF's. All Adverse Events and Device Deficiencies will be reviewed by Medtronic Safety Representative. Safety Representative will ensure the timely review and reporting of all events. Safety assessment will be documented in the safety database. The types of events and reporting requirements are described in section 11 below.

Product Complaint:

Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been released for distribution. Any complaint involving the possible failure of a device, labeling or packaging to meet any of its specifications is subject to reporting. Devices/products used in this study are commercially available in the countries participating in the study. Product complaints are not within the scope of this CIP and should be reported in addition to the Adverse Event reporting requirements. It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product, promptly.

9.9. Recording Data

The following table (Table 4) lists out the data collection requirements for each visit related to the study.

Table 4. Data Collection Requirements

	Baseline / Pre-Operative (data from most recent assessment from planned implant date preferred, not exceeding 60 days)	**Implant**	**Discharge** (date of discharge or 7 days post procedure, whichever comes first)	**3-6 month Follow Up** (data reported from 90 days up to 210 days post procedure, whichever comes later)	**12 month Follow Up** (data reported up to day 395 (365 +/- 30 days) post procedure date will be collected)
Inclusion/Exclusion Criteria	X				
PIC	X				
Patient demographics	X				
Pre-operative clinical history	X				

	Baseline / Pre-Operative (data from most recent assessment from planned implant date preferred, not exceeding 60 days)	Implant	Discharge (date of discharge or 7 days post procedure, whichever comes first)	3-6 month Follow Up (data reported from 90 days up to 210 days post procedure, whichever comes later)	12 month Follow Up (data reported up to day 395 (365 +/- 30 days) post procedure date will be collected)
Mitral Valvular Lesion and Risk Factors	X				
Cardiac Rhythm Assessment	X		X	X	X
Heart Failure Symptoms	X		X	X	X
NYHA Classification	X		X	X	X
Medications	X		X	X	X
Echocardiography including MR grade, mitral gradient, coaptation, LVEF, LVEDD, LAD and tricuspid and aortic valve assessments	X	X(1)	X	X	X
Implant Details		X			
Concomitant Procedures		X			
Re-operation			X	X	X
Serious Adverse Events including MACCE (as defined in section 11.1)		X	X	X	X
Device Deficiency		X	X	X	X
Death	As they occur				
Protocol Deviation					
Study Exit					X

(1) TEE specific parameters will be collected for TEE done at implant

9.9.1. Enrollment (Baseline) Visit

Besides the PIC and the meeting of the in/exclusion criteria, the following information will be collected:

- Demographics such as age and gender will be collected after enrolling subject
- Medical History such as etiology and history of previous surgical intervention will be documented
- Cardiac rhythm will be documented, measured as per standard practice (ECG/Holter)
- Heart failure symptoms (such as dyspnea, persistent coughing, edema, fatigue, nausea, orthopnea, confusion, increased heart rate) will be collected and results of physical examination (such as systolic and diastolic blood pressure, NYHA class) will be documented
- Evaluation of the mitral valvular lesion will be done and documented (Rheumatic, Ischemic, etc)
- Medication – The drug therapy provided to the subject at the enrollment visit will be documented

- Echocardiography – Transthoracic echo (TTE) data will be collected, documenting mitral valve regurgitation grade, mitral gradient and coaptation, right/left atrial, ventricular size and functional information (including aortic and tricuspid evaluation), etc.

Data from the most recent assessment before the planned implant date will be preferred, not exceeding 60 days.

9.9.2. Implant Visit

The implant will be performed as per surgeon's discretion and standard practice. The following information will be collected during the implant procedure.

- Details of surgical approach and procedural complexity (cross-clamp time, concomitant procedures, etc) will be documented
- Mitral valve pathology (valve dilatation, calcification, prolapse, etc) and leaflet segments affected (A1, A2, A3, P1, P2, P3) will be documented
- Details of mitral repair along with the ring/band annuloplasty (papillary muscle repair, chordal replacement or shortening, etc) and sizing of mitral valve annulus will be documented
- Serious Adverse Events including MACCE (as defined in section 11.1) during the implant will be documented, and an Adverse Event form will also be filled out
- Echocardiography – Transoesophageal echo (TEE) data will be collected, documenting various TEE parameters routinely evaluated during annuloplasty procedure.

9.9.3. Discharge Visit

This visit will be conducted at date of discharge or 7 days post procedure, whichever comes first. The following data are to be collected:

- Cardiac rhythm will be documented, measured as per standard practice (ECG/Holter)
- Heart failure symptoms (such as dyspnea, persistent coughing, edema, fatigue, nausea, orthopnea, confusion, increased heart rate) will be collected and results of physical examination (such as systolic and diastolic blood pressure, NYHA class) will be documented
- Medication – The drug therapy provided to the subject at discharge visit will be documented
- Serious Adverse Events including MACCE (as defined in section 11.1) since the implant will be documented, and an Adverse Event form will also be filled out
- Echocardiography – Transthoracic echo (TTE) data will be collected, documenting mitral valve regurgitation grade, mitral gradient and coaptation, right/left atrial, ventricular size and functional information (including aortic and tricuspid evaluation), etc.

9.9.4. 3-6 month Follow Up

This visit will be conducted between 90 days up to 210 days post procedure, whichever comes later. The following data are to be collected:

- Cardiac rhythm will be documented, measured as per standard practice (ECG/Holter)
- Heart failure symptoms (such as dyspnea, persistent coughing, edema, fatigue, nausea, orthopnea, confusion, increased heart rate) will be collected and results of physical examination (such as systolic and diastolic blood pressure, NYHA class) will be documented
- Medication – The drug therapy provided to the subject since last visit will be documented

- Serious Adverse Events including MACCE (as defined in section 11.1) since the implant will be documented, and an Adverse Event form will also be filled out
- Echocardiography – Transthoracic echo (TTE) data will be collected, documenting mitral valve regurgitation grade, mitral gradient and coaptation, right/left atrial, ventricular size and functional information (including aortic and tricuspid evaluation), etc.

9.9.5. 12 month Follow Up

This visit will be conducted up to 395 days (365 days +/- 30 days) post procedure. The following data are to be collected:

- Cardiac rhythm will be documented, measured as per standard practice (ECG/Holter)
- Heart failure symptoms (such as dyspnea, persistent coughing, edema, fatigue, nausea, orthopnea, confusion, increased heart rate) will be collected and results of physical examination (such as systolic and diastolic blood pressure, NYHA class) will be documented
- Medication – The drug therapy provided to the subject since last visit will be documented
- Adverse Events since last visit will be documented, and an Adverse Event form will also be filled out
- Echocardiography – Transthoracic echo (TTE) data will be collected, documenting mitral valve regurgitation grade, mitral gradient and coaptation, right/left atrial, ventricular size and functional information (including aortic and tricuspid evaluation), etc.

9.9.6. Source documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include but not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments such as hospital monitoring equipment, Holter portable document format (PDF) reports, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medicotechnical departments involved in the clinical trial.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical study.

The site is responsible to record all trial related source data enabling the sponsor to reconstruct the complete course of the clinical trial. Source data will be transcribed to and reported through the CRF accordingly. A source data identification list will be provided to the sponsor for approval prior to commencing the clinical part of the trial. The list will be filed in the investigator site file.

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

9.10. Deviation Handling

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study in accordance to the protocol or the Investigator agreement. The investigator is not allowed to deviate from these documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Examples of protocol deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain EC/IRB approval before the start of the study
- Subject did not meet inclusion/exclusion criteria
- Source data permanently lost
- Enrollment of subjects during lapse of EC/IRB approval

Investigators should obtain prior approval from Medtronic before initiating any change or deviation from the CIP, except where necessary to protect the life or physical wellbeing of a subject in an emergency situation. Such approval shall be documented in writing and maintained in the investigator site files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (eg. subject did not attend scheduled follow-up visit).

Deviations will be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations should be reported to Medtronic vide the study Deviation eCRF (1 eCRF for each protocol deviation). Relevant information for each deviation will be documented on a deviation form completed by site personnel and reviewed by the Investigator.

Investigators should report the following deviations to Medtronic and their reviewing EC/IRB in accordance with reporting requirements of local EC/IRB:

- Failure to obtain written informed consent
- Deviations to protect the life or physical well-being of a subject in an emergency

In addition, Investigators are required to adhere to local EC/IRB procedures for reporting deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be warranted such as amending the CIP, in accordance with Medtronic SOPs. Repetitive or serious investigator non-compliance may represent a need to initiate a corrective action plan, which may include suspension of enrollment or termination of the investigator's or site's participation in the study.

Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in- or deviation from the CIP. In case of any deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC/IRB and regulatory authority must also be obtained before implementation. The investigator shall timely contact the Clinical Manager for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the CIP do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC/IRB, if applicable.

9.11. Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the registry through the last follow-up visit at 12 months. Subjects who discontinue participation prematurely after attempted implant will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total study subjects. If a study subject is discontinued from the study early, the reason for discontinuation should be documented in the subject file and a Study Exit eCRF must be completed. If discontinuation is because of safety concerns, the subject shall be asked to be followed for collection of ongoing safety data outside the study. Any data collected after the exit date will not be analyzed as part of the study.

In case the subject undergoes device explant, the subject will be exited from the study.

The subjects will be exited from the study following their 12 month follow up visit. This 12 month visit will be primarily conducted via in-office visit and has a window period of additional 1 month, up to day 395 post implant. All adverse event information will be collected and reported during this follow up visit, as per timelines described above in section 11.2; subjects will be considered exited from the study on completion of their 12 month visit or when they are considered lost to follow up (after three failed attempts are made to contact the subjects).

The investigating site and Sponsor will make every effort to have all subjects complete the follow up visit schedule. A subject will not be considered lost-to-follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone and if contact via phone is not successful, a traceable letter from the Investigator must be sent to the subject's last known address. Should both telephone and mail efforts to contact the subject be unsuccessful, the subject's primary physician should be contacted. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow-up must be documented in the subject's medical records.

If a subject discontinues the study at any time, is withdrawn from the study early, or completes all protocol required follow-up they should then be followed per the local standard of care for their condition.

10. Risks and Benefits

10.1. Potential Risks

This study does not require any additional interventions other than the standard of care, therefore no risks other than the risks typically associated with a routine annuloplasty procedure and follow-ups are anticipated. All products in the study are commercially available when the study is in effect and will be used in accordance with approved labeling.

While infrequent, certain complications have been reported when using annuloplasty systems. As per the Instructions-For-Use of the product, these include the following:

- Uncorrected or recurrent regurgitation
- Stenosis
- Dehiscence
- Hemolysis (even with mild regurgitation)
- Low cardiac output
- Heart block
- Systolic anterior motion (SAM) and left ventricular outflow tract obstruction (LVOTO)
- Damage to coronary arteries
- Endocarditis
- Thrombosis
- Thromboembolism
- Anticoagulant-related bleeding or hemorrhage
- Ring fracture
- Leaflet perforation

These complications could lead to:

- Reoperation
- Explant of the annuloplasty system
- Permanent disability
- Death

There might be additional risks associated with any concomitant procedures as conducted per standard treatment of the subject which are not listed here.

In case of occurrence of adverse events, the subjects will be treated and followed up as per standard of care, as mandated by the treating physician.

10.2. Potential Benefits

There is no immediate benefit associated with participating in the study. However, the evidence collected in this study may help to improve future care.

10.3. Risk-Benefit Rationale

This study is a non-interventional study, with no additional risks to the subject relative to participation in the study, and hence, the potential benefits outweigh the risks.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

Adverse Event (AE) ***(ISO 14155:2011, 3.2)***

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

NOTE 1 This definition includes events related to the investigational medical device 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 investigational medical devices.

Adverse Device Effect (ADE) *(ISO14155:2011 3.1)*

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

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device

NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE) *(ISO 14155:2011, 3.37)*

Adverse event that

a) led to a death

b) led to serious deterioration in the 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 or prolonged 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

c) led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE) *(ISO14155:2011 3.36)*

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

Unanticipated serious adverse device effect (USADE) ***(ISO14155:2011 3.42)***

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

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

Major adverse cardiac and cerebrovascular events (MACCE)

- All-cause mortality
- Myocardial infarction
- Emergent cardiac surgery or re-intervention
- Stroke
- Hospitalization for Heart Failure

Device Deficiency (DD) ***(ISO14155:2011 3.15)***

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE *Device deficiencies include malfunctions, use errors and inadequate labeling*

11.2. Reporting of Adverse Events and Device Deficiencies

Investigator reporting requirement

Report	Submit to	Description/Constraints
All SAE,SADE, USADE	Monitor and Sponsor	Investigator shall report all SAEs, SADEs and USADEs to the Sponsor and monitor promptly of their occurrence. (*Indian GCP section 3.3.4.3)* It is recommended for investigator to report all SAEs, SADEs and USADEs to the sponsor within 24 hours. For reported deaths the investigator shall supply any additional information e.g. autopsy report and terminal medical reports. *(Indian GCP section 3.3.4.5)*
All SAE, SADE, USADE	EC	Investigator shall report all SAEs, SADEs and USADEs to the EC promptly of their occurrence. *(Indian GCP section 3.3.4.3)* For reported deaths the investigator shall supply any additional information e.g. autopsy report and terminal medical reports. *(Indian GCP section 3.3.4.5)* It is recommended for investigator to report all SAEs, SADEs and USADEs to EC within 7 working days unless a stricter timeline is required by the EC.
All Device Deficiency	Monitor and Sponsor	Investigator shall report all DDs to the Sponsor and monitor promptly of their occurrence. It is recommended for investigator to report all DDs to the sponsor within 24 hours.

New information that may adversely affect safety of the subjects or the conduct of the study	EC, monitor and sponsor	Investigator shall promptly report new information that may adversely affect safety of the subject or the conduct of the study. (Indian GCP section 3.3.4.4)

Sponsor reporting requirement

Report	Submit to	Description/Constraints
USADE	DCGI , Chairman of the EC	The report of the serious adverse event, after due analysis, shall be forwarded by the Sponsor to the Licensing Authority and Chairman of the Ethics Committee within 15 days the sponsor became aware of the serious adverse event. In case of the site directly reporting the USADE to EC, the Sponsor requirement to report to the EC is considered to be sufficiently met.

Non reportable events

The events listed in the table below are expected for patients undergoing cardiac surgery, and do not need to be reported as an AE, unless they occur outside of the stated timeframe, are otherwise considered to be an AE according to the investigator, or are suspected or confirmed to be device-related.

Body Category	**Occurrence**	**Timeframe (hours) post procedure**
Hematologic	Blood transfusion and anemia occurring during the procedure within expected ranges (part of the regular hospital protocol)	0
Hematologic	Any bleeding during the procedure	0
Hematologic	Any bleeding after procedure with < 3 units blood transfusion, or < 1 liter blood loss	24
Cardiac	Short transient episode of arrhythmia (including ventricular fibrillation) during procedure	0
Central Nervous System	Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Central Nervous	Temporary change in mental status (other than	72

Body Category	Occurrence	Timeframe (hours) post procedure
System	TIA/stroke) not requiring additional medical interventions or new medical assessments (e.g. CT)	
Central Nervous System	Dizziness and/or lightheadedness with or without treatment	24
Central Nervous System	Headache with or without treatment	72
Central Nervous System	Sleep problems or insomnia with or without treatment	120 (5 days)
Respiratory/Pulmonary	Mild dyspnea or cough with or without treatment	72
Respiratory	Oxygen supply after extubation / "forced breathing therapy"	48
Gastrointestinal	Diarrhea with or without treatment	48
Gastrointestinal	Obstipation / Constipation with or without treatment	72
Gastrointestinal	Anesthesia-related nausea and/or vomiting with or without treatment	24
Body Temperature	Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Body Temperature	Low body temperature	6
Pain	Pain (e.g. back, shoulder) related to laying on the procedure table with or without treatment	72
Pain	Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain	Pain in throat and/or trachea due to intubation	72
Skin and subcutaneous System	Mild to moderate bruising or ecchymosis	168 (7 days)
Respiratory	Atelectasis / Pleural Effusion not requiring punctuation	168 (7 days)
General	Edema resulting in weight increase up to 4 kg / 9lbs from baseline	168 (7 days)

12. Data Review Committees

There will be no Data Monitoring Committee (DMC) or Clinical Events Committee (CEC) used in this study. There will be a Medical Advisor assigned to this study, who will provide guidance on safety issues when escalated from the safety representative and is consulted on planning and documentation for the study. The contact information will be kept in the study roster.

13. Statistical Design and Methods

The statistical analyses will be performed by Medtronic employed statisticians. Three study populations are defined:

- Enrolled: Composed of all patients who signed the Patient Informed Consent Form.
- Attempted Implant (AT): Composed of all enrolled subjects who are attempted for a Profile 3D™ or CG Future® Annuloplasty system implantation. Time zero begins at the date of attempted procedure.
- Implanted (IMP): Composed of all AT subjects who had either a Profile 3D™ or CG Future® Annuloplasty system implanted. Time zero for implanted subjects begins at the date of implant procedure.

All data collected from enrolled, attempted implant, and implanted subjects will be utilized in the analyses as appropriate. Analyses of the primary and secondary endpoints will be descriptive, and no statistical hypothesis tests will be performed.

All continuous variables will be summarized as the number of subjects, means, standard deviations, medians, minimums, maximums, and interquartile ranges. Categorical variables will be summarized as frequencies and percentages.

Additional details of planned statistical analysis will be specified in Statistical Analysis Plan (SAP). Any deviations from the original statistical plan will be summarized in the Clinical Study Report(s) (CSRs), along with the justification for the deviations.

13.1. Missing/Unused/Unauthentic Data

Every effort will be undertaken to minimize missing data, unused data and unauthentic data. Unless otherwise specified, no statistical techniques will be used to impute missing data. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data. Data management procedures defined in Section 15.2 will be followed to minimize unauthentic data in the analysis datasets. Handling of unused data will be defined in the Statistical Analysis Plan.

13.2. Subgroup Analysis

Details of planned subgroup analysis will be specified in Statistical Analysis Plan (SAP).

13.3. Interim Analysis

An interim summary of the data is planned when all enrolled and implanted subjects have had the opportunity to be followed through (are eligible for) the discharge visit. This is an observational study, no

statistical hypothesis tests will be performed, and there are no pass/fail criteria for the results of this study.

13.4. Sample Size Determination

The sample size of 200 subjects who are eligible and intended to be implanted with a Profile 3D™ or CG Future® Annuloplasty system in the surgical repair procedure is adequate and appropriate for the evaluation of local evidence and obtaining real world data on clinical outcomes following implantation of these two products. This sample size was not statistically derived as this is not a hypothesis driven study.

13.5. Primary Endpoints

The primary endpoints are the following clinical outcomes at 12 months post procedure:

1. Improvement in MR (grade)

   Mitral valve function will be based on site echocardiographic recordings. For each subject with paired data, the change from baseline (improved, no change, worsened) will be evaluated at 12 months. The primary endpoint of improvement in MR (grade) will be presented with frequencies and percentages of subjects with improved MR at 12 months. The two-sided 95% exact binomial confidence interval of the overall percent of subjects with improved MR at 12 months will also be reported.

2. All-cause mortality

   A Kaplan-Meier analysis will be performed. The endpoint is descriptive and no statistical hypothesis test will be performed.

13.6. Secondary Endpoints

The secondary endpoints are as follows:

1. Characterization of patient demographics and pathophysiology of mitral valve disease

   Baseline demographic and clinical variables will be summarized. Descriptive statistics will be provided.

2. Improvement in MR grade at discharge and first follow up (3-6 months)

   Mitral valve function will be based on site echocardiographic recordings. For each subject with paired data, the change from baseline (improved, no change, worsened) will be evaluated at discharge and 3-6 months. The secondary endpoint of improvement in MR (grade) will be presented with frequencies and percentages of subjects with improved MR at discharge and 3-6 months. The two-sided 95% exact binomial confidence interval of the overall percent of subjects with improved MR at discharge and 3-6 months will also be reported.

3. Improvement in NYHA functional class at discharge, first follow up (3-6 months) and second follow up (12 months) compared to baseline

   For each subject with paired data or who died prior to visit, the change from baseline (improved, no change, worsened or died) will be calculated at discharge, 3-6 months, and 12 months. The endpoint of improvement in NYHA class will be presented with frequencies and percentages of subjects with improved NYHA at discharge, 3-6 months, and 12 months. The two-sided 95% exact binomial confidence interval of the overall percent of subjects with improved NYHA class at these time intervals will also be reported.

4. Hospitalization for Heart Failure at 6 months and at 12 months post procedure

A Kaplan-Meier analysis will be performed. The duration of hospitalization for heart failure will be summarized. The endpoint is descriptive and no statistical hypothesis test will be performed.

5. Mitral valve re-intervention at discharge, 6 months and at 12 months post procedure

   A Kaplan-Meier analysis will be performed. The endpoint is descriptive and no statistical hypothesis test will be performed.

6. Stroke at 6 months and at 12 months post procedure

   A Kaplan-Meier analysis will be performed. The endpoint is descriptive and no statistical hypothesis test will be performed.

7. New onset of Atrial Fibrillation, as evaluated through follow up ECG at discharge, first follow up (3-6 months) and at second follow up (12 months)

   The number (and percent) of subjects with new onset of Atrial Fibrillation will be evaluated at discharge, 3-6 months, and 12 months. Descriptive statistics will be provided.

8. Number of attempts required for procedural success, and bypass time as a measure of procedural complexity

   The number of attempts (per subject) required for procedural success and the bypass time will be summarized. Descriptive statistics will be provided.

14. Ethics

14.1. Statement(s) of Compliance

- The study will be conducted in accordance with the protocol and ethical principles that have their origin in the Declaration of Helsinki, and India GCP.
  - The study will not begin until EC/IRB approvals as required are received.
  - Any special requirements imposed by EC/IRB will be followed for the respective sites.
  - The Name(s), title(s), address(es), and contact numbers of the investigator(s) who are responsible for conducting the study, along with their consent letter(s) (Investigator Statement),will be listed and kept separate from the CIP and will be updated by the sponsor.
  - The Name(s), address(es) and contact numbers of the institution(s) particulars of the head(s) of the institution(s), will be kept separate from the CIP. The sponsor will maintain an updated list.
- If any action is taken by an EC/IRB with respect to the investigation, that information should be forwarded to the sponsor.

15. Study Administration

15.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical investigation per regulations. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable local regulatory requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' medical records (and other source data/documentation) upon request as per the Subject Informed Consent and Clinical Trial Agreement.

Monitoring Visits

Frequency of monitoring visits will be based upon subject enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Monitoring for the study will be done in accordance to the study monitoring plan. Monitoring visits may be conducted to assess the investigator's adherence to the CIP, including but not limited to Ethics Board approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

15.2. Data Management

15.2.1. Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection. The database is located on a secure server at a Medtronic facility located in the United States. All users will be trained on the use of the database prior to obtaining access. Once access is granted, users will have a unique User ID and will create their own password. Data stored electronically shall be maintained in compliance with 21CFR Part 11. The database for this trial will be maintained for life of the medical device plus one year, or 15 years, whichever is longer according to corporate policy and record retention schedule.

15.2.2. Data Collection

It is the responsibility of the participating Investigator to ensure the quality of the data being collected. Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation of Tasks List. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the trial.

The investigator will electronically sign each eCRF.

The EDC system maintains an audit trail on entries, changes or corrections in eCRFs, once the eCRF is saved as complete. If changes are made to an already signed eCRF, the investigator shall re-sign this eCRF.

15.2.3. Data Validation

The sponsor and/or assigned designee will be responsible for the processing and quality control of the data (data management) per the Data Management Plan, which describes the procedures for data review, database cleaning and issue/resolution of data queries. Data will be collected and stored in a validated, password protected database. Data analysis will be conducted utilizing validated software and analysis programs by qualified biostatisticians.

Trial data collected will be monitored and verified against source documents in accordance with ISO14155:2011 guidelines and international standards. Any data discrepancies will be addressed through queries posted within the EDC system.

15.3. Direct Access to Source Data/Documents

The sponsor or a regulatory authority, may audit the study site to evaluate the conduct of the study and to ensure compliance to GCP, the CIP, and applicable local regulatory requirements. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Board review and regulatory inspection(s) by providing direct access to source data/documents.

15.4. Confidentiality

All records and other information about subjects participating in this study will be treated as private and confidential, investigator will keep full patient lists or records.

Medtronic will collect data in such a way that no subject can be identified. Participating subjects will not be identified by name in any published reports about the study.

15.5. Liability

Since this is a post market study with no investigational devices, no compensation will be provided to subjects for participating in the study or as part of the study.

Medtronic 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 a Clinical Trial insurance statement/certificate will be provided to the Medical Institution and Ethics Committee.

15.6. CIP Amendments

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the investigators to obtain approval from their respective EC/IRB. Where applicable, minor administrative amendments to the Clinical Investigation Plan will also be submitted to the EC /IRB for notification or approval per EC requirements.

15.7. Record Retention

The site is responsible for the maintenance of the records listed below:

- All essential correspondence that pertains to the study, including the Ethics Committee, sponsor, monitor, or the investigator that pertains to the investigation, including required reports.
- Signed and dated original clinical trial agreement.
- Insurance documents.
- All approved versions of the Clinical investigational plan.

- All original signed copies of the PIC's along with all other essential documents as approved by the Ethics Committee.
- Site personnel training documentation and delegated task list.
- Ethics Committee approval/Notification documents, as applicable.
- Relevant Medical history towards subject eligibility.
- Current curriculum vitae (signed and dated) of investigators and other members of Investigation site team per the DTL.
- Records of AEs and ADEs reported to Sponsor.
- Final Clinical Study Report (CSR)

Records are subject to be audited by Medtronic for compliance and all study related documents and material should be maintained for a period of three years after the completion of the study.

Investigational sites are responsible for ensuring that the participating investigator and other site staff are appropriately licensed/qualified. Medtronic will review these records to assess compliance to institutional policy and required regulations

15.8. Publication and Use of Information

The Medtronic study team will collaborate to publish the results of the study in an appropriate/highest impact local (Indian) and global publications. Medtronic may implement a publication committee to effectively manage and oversee the primary, secondary and ancillary publications generated from the study while complying with all applicable guidelines and policies.

Publications and presentations referring to the PRESERVE-Mitral Study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating Investigational Centers:

Authorship on any publication(s) resulting from this study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Medtronic owns the data of the PRESERVE-Mitral study, a single Investigational Center may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records. Participating subjects will not be identified by name in any published reports about the study.

15.9. Suspension or Early Termination

Medtronic may decide to suspend or prematurely terminate the study (eg, because of a business decision). If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects or their legal representative. In case of early termination, subjects need to be followed until at least 30 days after the initial procedure.

Medtronic may decide to suspend or prematurely terminate an Investigational Center (eg, in case of expiring approval of the reviewing EC/IRB, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an Investigational Center is suspended or prematurely terminated, Medtronic shall promptly inform the clinical investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects or their legal representative. In case of early termination, subjects need to be followed until at least 30 days after the initial procedure.

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17. Appendices

Appendix L.1.

Instructions-for-Use – Profile 3D™ Annuloplasty Ring

1 DEVICE DESCRIPTION

The Medtronic PROFILE 3D™ Annuloplasty Ring, Model 680R (hereafter referred to as PROFILE 3D™ Ring) consists of a titanium core overmolded with silicone and covered with polyester fabric. The ring must be implanted in the mitral position. The ring is marked at three points by colored sutures; two markers correspond to the trigones of the mitral valve and one identifies the midpoint of the device. The device size is identified by the inside diameter of the ring at its widest point. The titanium core enables radiographic visualization of the device.

Nonclinical testing has demonstrated the PROFILE 3D™ Ring is Magnetic Resonance (MR) Conditional. It can be scanned safely according to the conditions presented in Table 1.

Patients with the PROFILE 3D™ Ring may safely undergo MRI for Normal Mode of the MR System as defined in the IEC Standard 60601-2-33. MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the PROFILE 3D™ Ring. Therefore, it may be necessary to optimize MR imaging parameters for the presence of this implant. See Table 1 for maximum distortion distances for spin echo and gradient echo sequences. These values are based upon nonclinical testing at 3T according to ASTM F2119-01.

[a]In nonclinical testing according to ASTM F2182-02a when the local SAR is normalized to 1 W/kg for 15 minutes of MR scanning in a GE 64 MHz whole body transmit coil, and a Siemens TrioTim 3T whole body transmit coil.

2 INDICATIONS

The PROFILE 3D™ Ring is indicated for the reconstruction and/or remodeling of pathological mitral valves. Valvular insufficiency and/or stenosis may be corrected by appropriate repair and annular remodeling.

3 CONTRAINDICATIONS

- Heavily calcified valves.
- Valvular retraction with severely reduced mobility.
- Active bacterial endocarditis.

4 WARNINGS

- **For single use only.**
- Only surgeons who have received adequate training to determine whether incompetent,stenotic, or diseased heart valves are capable of being repaired or replaced should use this device.
- Only surgeons who have received appropriate training in valve repair, including ring implant and sizing techniques, should use this device.
- Correct annuloplasty ring sizing is an important element of a successful valve repair. Undersizing the ring can result in valve stenosis, ring dehiscence, and/or ring fracture. Oversizing the ring can result in valve regurgitation and/or ring fracture.
- Care should be taken that sutures are not placed in atrial tissue, as this may result in impairment of the cardiac conduction system.
- It is necessary to secure the ring into fibrous trigone tissue to maintain permanent attachment.
- Suture knots must be securely tied. Loose knots and long suture tails may be a source for hemolysis, thrombosis, or thromboembolism.
- Do not cut the ring. Resultant loose threads may be a source of hemolysis, thrombosis, and/or thromboembolism. In addition, resultant jagged edges of the stiffener may lead to tissue trauma.
- Do not alter or deform the ring to conform to annular anatomy as this could lead to ring fracture, possible valve regurgitation, or stenosis.
- Do not squeeze the ring with sharp instruments as this may damage the surface of the stiffener, which may result in ring fracture and possible mitral regurgitation.
- Intraoperative and/or postoperative echocardiography should be used to evaluate the effectiveness of the valve repair. Minimizing regurgitation and systolic anterior motion (SAM) are important elements of an effective repair.
- Surgeons who use annuloplasty rings should be current on all anticoagulation regimens.
- When postoperative anticoagulant therapy is used, the patient's anticoagulation status should be carefully monitored.
- Patients with intra-atrial thrombi or a giant left atrium may benefit from long-term anticoagulation therapy.
- The surgeon may desire that patients in atrial fibrillation remain on anticoagulation therapy until sinus rhythm is established.
- The ring is indicated for use in the mitral position only. Use in the tricuspid position may result in ring fracture, conduction system damage, tricuspid regurgitation, and/or ring dehiscence.

5 PRECAUTIONS

- Do not use cutting edge needles, as they may damage the annuloplasty device potentially leading to ring dehiscence, ring fracture, and possible mitral regurgitation.

6 POTENTIAL ADVERSE EVENTS

While infrequent, certain complications have been reported when using annuloplasty rings.

These include the following:

- Uncorrected or recurrent regurgitation
- Stenosis
- Ring dehiscence
- Hemolysis (even with mild regurgitation)
- Low cardiac output
- Heart block
- Systolic anterior motion (SAM) and left ventricular outflow tract obstruction (LVOTO)
- Damage to coronary arteries
- Endocarditis
- Thrombosis
- Thromboembolism
- Anticoagulant-related hemorrhage
- Ring fracture
- Leaflet perforation

The potential for these complications should be considered when selecting the most beneficial surgical procedure for each patient.

To avoid or minimize occurrence of these adverse events, the annuloplasty repair, including sizing and implantation, should be conducted in accordance with the methods prescribed in these Instructions for Use by surgeons with appropriate training and experience in valve repair.

7 INDIVIDUALIZATION OF TREATMENT

To allow for healing and incorporation of the annuloplasty ring by host tissue, regardless of cardiac rhythm, postoperative anticoagulation therapy should be considered for at least six weeks following surgery.

8 PATIENT COUNSELING INFORMATION

Patients with annuloplasty rings who undergo dental or other potentially bacteremic procedures must be considered for prophylactic antibiotic therapy.

9 HOW SUPPLIED

9.1 Packaging

The PROFILE 3D™ Ring is available in the following sizes for the mitral position: 24, 26, 28, 30, 32, 34, 36, 38, and 40 mm. The package contains a single annuloplasty ring assembly consisting of the device and holder (Figure 1) packaged in sterile, double-aseptic transfer trays. The packaging system is designed to ease placement of the device into the sterile field. The ring assembly is sterile if the trays are undamaged and unopened. The outer surfaces of the outer tray are NONSTERILE and must not be placed in the sterile field.

9.2 Storage

Store the product in its original packaging, including the outer shelf carton, in a clean, cool, and dry area to protect the product and minimize the potential for contamination.
The sterility and nonpyrogenicity of the PROFILE 3D™ Ring are validated to remain unaffected until the Use By date identified on the shelf carton, provided the trays are not opened or damaged.

10 DIRECTIONS FOR USE

10.1 Sizing

The Medtronic PROFILE 3D™ Ring Sizer Set, Model 7680S is used to select the proper
PROFILE 3D™ Ring size for repair of the mitral valve. Sizers are reusable; however, they must be cleaned and sterilized by autoclave (steam) prior to each use.
Proper ring size selection is an important part of valvular annuloplasty to help restore proper valve function. Use the PROFILE 3D™ Ring Sizer Set for size selection. The metal section of the sizer is malleable, allowing the surgeon to align the sizers with the valve annulus.
Warning:
- Do not use other manufacturers' annuloplasty sizers or sizers from other Medtronic annuloplasty products to size the PROFILE 3D™ Ring. Other annuloplasty sizers may not indicate the appropriate PROFILE 3D™ Ring size.
- The sizers are provided NONSTERILE; they must be cleaned and sterilized prior to use.

Mitral Valve
To determine the proper PROFILE 3D™ Ring size, both the distance between the annular trigones and the area of the anterior leaflet must be measured. First, lower the sizer onto the valve annulus and align the sizer notches with the annular trigones. Second, gently extend the anterior leaflet and cover its surface with the selected sizer. The sizer that has a notch spacing most nearly matching the intertrigonal distance (Figure 2) and a surface area most nearly matching that of the anterior leaflet corresponds to the size of the ring that should be selected. Either end of the sizer may be used for sizing.

10.2 Handling and Preparation Instructions

- Open the box and remove the product literature and Patient Registration Form.
- Remove the double-aseptic transfer tray containing the ring mounted to the holder.
- Inspect the trays ensuring they have not been opened or damaged. The ring assembly is sterile as long as the inner tray has not been compromised. If the inner tray is damaged, do not implant the ring.
- If the outer tray is damaged, the exterior surface of the inner tray may not be sterile.
- Open the outer transfer tray, and while still holding the bottom of the outer tray, pass the inner tray into the sterile field.
- The inner tray should be opened only in the sterile field.

10.3 Device Implantation

The PROFILE 3D™ Ring assembly may be used with or without the Medtronic Annuloplasty Handle, Model 7686 (provided separately).
Warning: The handle must be cleaned and sterilized prior to use.
To use the handle, align and engage the sterile handle into the snap fit cavity of the holder (Figure 3). The thin section of the handle is malleable, allowing the surgeon to align the device with the annulus.
Note: The handle must be inserted into the side of the holder with the snap fit cavity and the printed text.
Remove the serial number identification tag (Figure 4) and record the serial number in the patient's record. Verify that the serial number matches the serial number on the Patient Registration Form.
Warning: The serial tag must be removed from the ring for proper function. Do not cut or tear the ring fabric during removal of the serial tag.
Mitral Suture Placement
Caution: The PROFILE 3D™ Ring is designed for implantation only with interrupted-suture techniques.
Place sutures in each trigone, approximately 4 mm in width. Place additional interrupted sutures, approximately 4 mm in width, in the anterior and posterior portions of the mitral annulus (Figure 5). A total of approximately 10 to 14 sutures should be placed in the annulus.
Warning: Avoid placing sutures in the circumflex coronary artery.
Note: Pledgets may be used for trigone sutures and midposterior annulus suture to reduce the possibility of ring dehiscence.
Ring Suture Placement
Orient the ring assembly to the mitral annulus (Figure 6).

Pass sutures through the ring, approximately 2 mm in width, entering at the bottom of the ring and exiting the periphery of the ring (Figure 7). Pass only one suture through each trigonal marker on the ring.
Holder/Handle Removal
Use the holder/handle to push the ring down onto the valve annulus while pulling back on the sutures. Using a scalpel, cut the retention sutures on the holder in the areas indicated (Figure 8). Remove the disposable holder and handle from the valve annulus (Figure 9).
Dispose of the holder.
Warning:
- Do not cut the ring fabric while cutting the holder retention sutures.
- The PROFILE 3D™ Ring holder must be removed from the ring at the end of the procedure for proper function. Under no circumstances should the holder remain attached to the ring.

Knots, Testing
Tie all knots around the device securely (Figure 10a and 10b), trim all excess sutures, and test valvular competency after removing the holder.
Warning: Suture knots must be securely tied. Loose knots and long suture tails may be a source of hemolysis, thrombosis, or thromboembolism.

10.4 Accessories

The PROFILE 3D™ Ring Sizer Set, Model 7680S is used to select the proper PROFILE 3D™ Ring size for repair of the mitral valve. Sizers are reusable; however, they must be cleaned and sterilized by autoclave (steam) prior to each use. Refer to the PROFILE 3D™
Ring Sizer Set Instructions for Use for detailed information on accessory use and sterilization.

Warning:
- Do not use other manufacturers' annuloplasty sizers or sizers from other Medtronic annuloplasty products to size the PROFILE 3D™ Ring. Other annuloplasty sizers may not indicate the appropriate PROFILE 3D™ Ring size.
- The sizers are provided NONSTERILE; they must be cleaned and sterilized prior to use.

Use only the Annuloplasty Handle, Model 7686 to interface with the holder. Refer to the Annuloplasty Handle Instructions for Use for detailed information on use and sterilization.
Warning: The handle is provided NONSTERILE; it must be cleaned and sterilized prior to use.

10.5 Sterilization

The ring is provided sterile (steam) on the holder and must not be resterilized. Rings that have been damaged or contaminated from patient contact should not be used.

11 REGISTRATION INFORMATION

Note: Patient registration does not apply in countries where patient privacy laws conflict with providing patient information, including countries from the EU.
A Patient Registration Form is included in each device package. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the device. Return the original form to the Medtronic address indicated on the form and provide the temporary identification card to the patient prior to discharge.

12 DISCLAIMER OF WARRANTIES

THE FOLLOWING DISCLAIMER OF WARRANTY APPLIES TO UNITED STATES CUSTOMERS ONLY:
DISCLAIMER OF WARRANTY
ALTHOUGH THE PROFILE 3D™ ANNULOPLASTY RING, MODEL 680R, HEREAFTER REFERRED TO AS "PRODUCT," HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, MEDTRONIC HAS NO CONTROL OVER THE CONDITIONS UNDER WHICH THIS PRODUCT IS USED. MEDTRONIC, THEREFORE, DISCLAIMS ALL WARRANTIES, BOTH EXPRESS AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. MEDTRONIC SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL, OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE, OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT, OR OTHERWISE. NO PERSON HAS ANY AUTHORITY TO BIND MEDTRONIC TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.
The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of
Warranty is held by any court of competent jurisdiction to be illegal, unenforceable, or in conflict with applicable law, the validity of the remaining portion of the Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.
THE FOLLOWING DISCLAIMER OF WARRANTY APPLIES TO CUSTOMERS OUTSIDE THE UNITED STATES:
DISCLAIMER OF WARRANTY ALTHOUGH THE PROFILE 3D™ ANNULOPLASTY RING, MODEL 680R, HEREAFTER
REFERRED TO AS "PRODUCT," HAS BEEN CAREFULLY DESIGNED, MANUFACTURED, AND TESTED PRIOR TO SALE, THE PRODUCT MAY FAIL TO PERFORM ITS INTENDED FUNCTION SATISFACTORILY FOR A VARIETY OF REASONS. THE WARNINGS CONTAINED IN THE PRODUCT LABELING PROVIDE MORE DETAILED INFORMATION AND ARE CONSIDERED AN INTEGRAL PART OF THIS DISCLAIMER OF WARRANTY. MEDTRONIC, THEREFORE, DISCLAIMS ALL WARRANTIES, BOTH EXPRESS AND IMPLIED, WITH RESPECT TO THE PRODUCT. MEDTRONIC SHALL NOT BE LIABLE FOR ANY INCIDENTAL OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, OR FAILURE OF THE PRODUCT, WHETHER THE CLAIM IS BASED ON WARRANTY, CONTRACT, TORT, OR OTHERWISE.
The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of
Warranty is held to be illegal, unenforceable, or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.

Figure 1

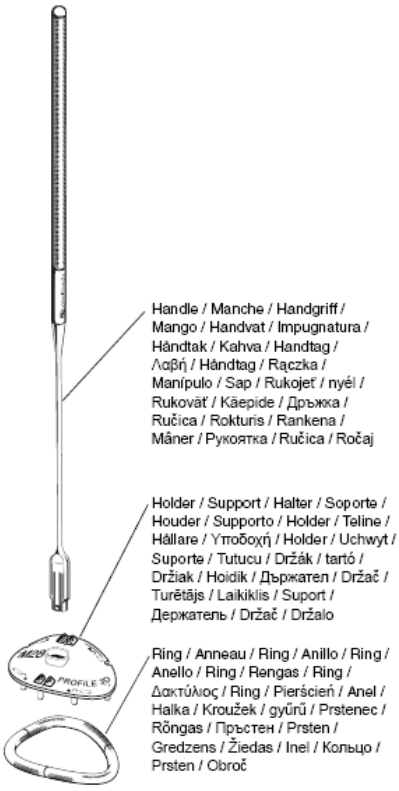


Figure 2

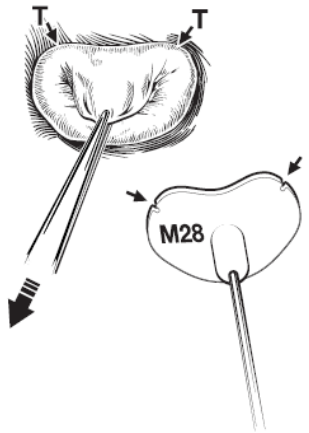
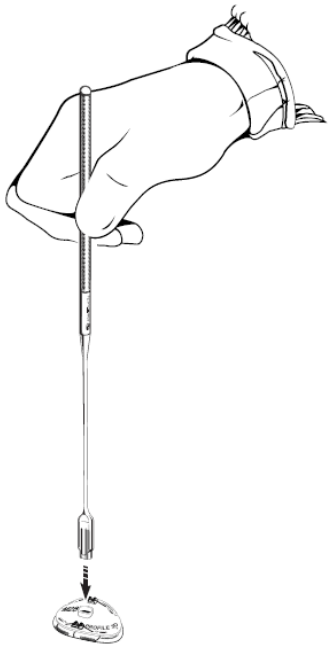


Figure 3



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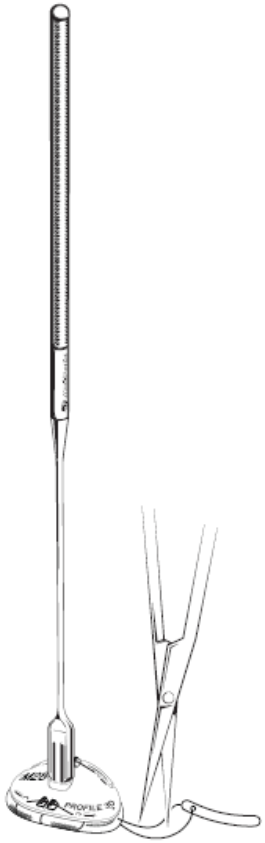

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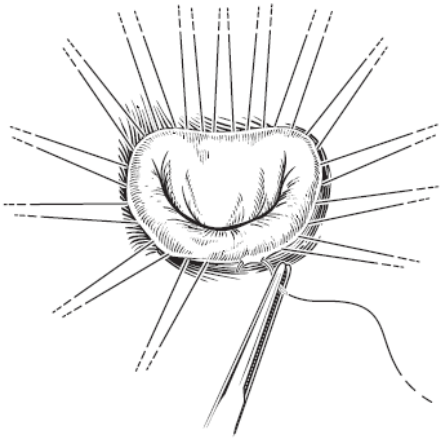

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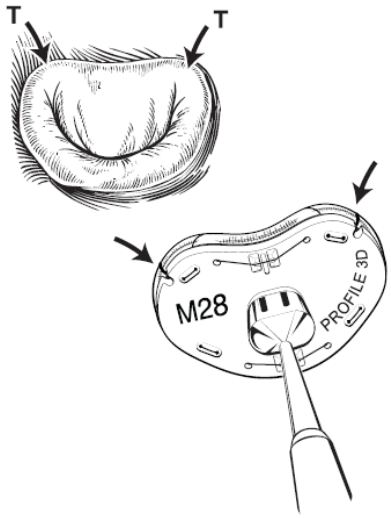

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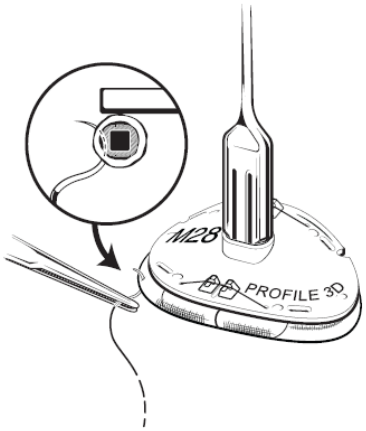

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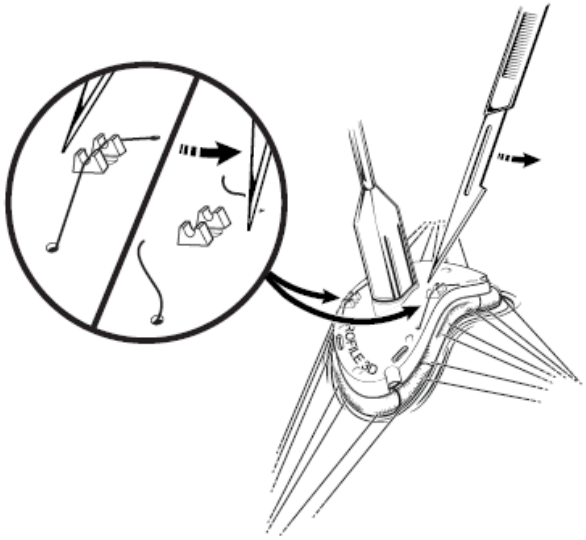


Figure 9

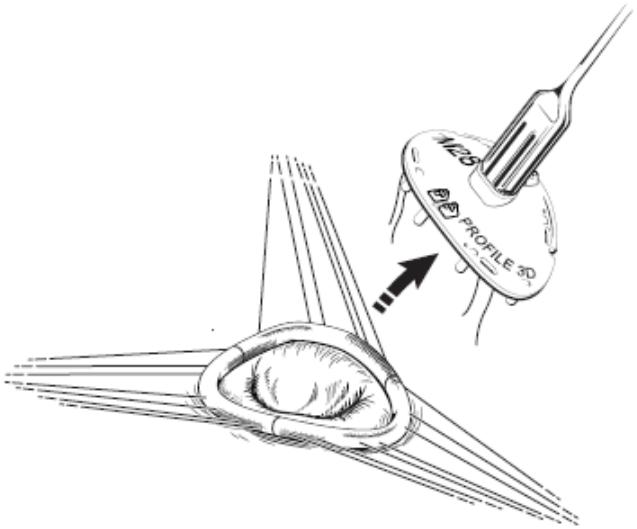
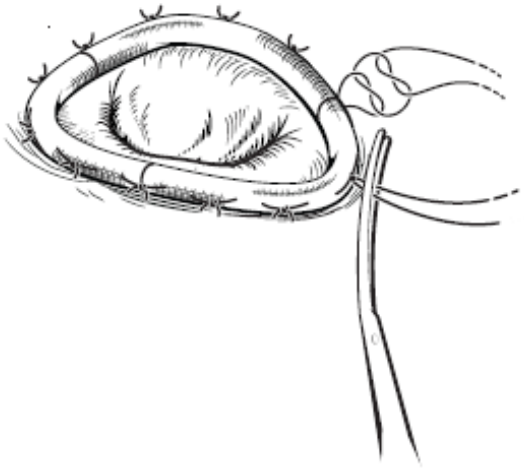


Figure 10a



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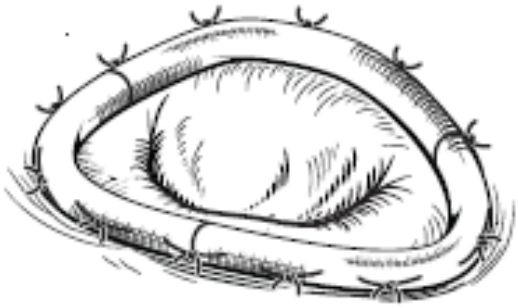

Instructions-for-Use – CG Future® Annuloplasty Ring/Band

1 DEVICE DESCRIPTION

The Medtronic CG Future® Annuloplasty Ring Model 638R and the Medtronic CG Future® Annuloplasty Band Model 638B (hereafter referred to as CG Future® Annuloplasty Ring/Band) consist of a MP35N wire overmolded with silicone and covered with polyester fabric. Both the ring and band must be implanted in the mitral position. The ring and band are marked at three points by colored sutures; two markers correspond to the trigones of the mitral valve and one identifies the midpoint of the device. The device size is identified by the inside diameter of the ring or band at its widest point. The MP35N wire allows radiographic visualization of the devices. The ring also includes a silicone marker, impregnated with barium sulfate, for radiographic visualization.

Nonclinical testing has demonstrated that the CG Future® Annuloplasty Ring/Band is MR (magnetic resonance) Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of δ3.0 tesla
- Spatial gradient field of δ3.9 T/m
- Maximum whole-body-averaged specific absorption rate (SAR) of 1.1 W/kg for δ20 minutes of scanning as read from equipment monitor

In nonclinical testing the CG Future® Annuloplasty Ring/Band produced a temperature rise of δ0.2°C at a maximum wholebody-averaged specific absorption rate (SAR) of 1.1 W/kg for δ20 minutes of MR scanning in a field strength of 3.0 tesla, GE Signa®1 LX 3.0 T MR System: multi-coil superconducting, actively shielded magnet housed in a 94 cm bore; gradient amplitude - 40 mT/m and slew rate - 150 T/m/s; VH3_M4 software. The maximum whole body SAR of 1.1 W/kg for δ20 minutes was read from the scanner console.

2 INDICATIONS

The CG Future® Annuloplasty Ring/Band are indicated for the reconstruction and/or remodeling of pathological mitral valves.

Valvular insufficiency and/or stenosis may be corrected by appropriate repair and annular remodeling.

3 CONTRAINDICATIONS

- Heavily calcified valves.
- Valvular retraction with severely reduced mobility.
- Active bacterial endocarditis.

4 WARNINGS

- **For single use only.**
- Only surgeons who have received adequate training to determine whether incompetent, stenotic, or diseased heart valves are capable of being repaired or replaced should use this device.
- Only surgeons who have received appropriate training in valve repair, including ring and band implant and sizing techniques, should use this device.

1 Signa® is a registered trademark of General Electric Corporation.

- Correct annuloplasty ring and band sizing is an important element of a successful valve repair. Undersizing the ring or band can result in valve stenosis, ring/band dehiscence, and/or ring/band fracture. Oversizing the ring or band can result in valve regurgitation and/or ring/band fracture.
- Care should be taken that sutures are not placed in atrial tissue, as this may result in impairment of the cardiac conduction system.
- It is necessary to secure the ends of the ring and band into fibrous trigone tissue to maintain permanent attachment.
- Suture knots must be securely tied. Loose knots and long suture tails may be a source for hemolysis, thrombosis, or thromboembolism.
- Do not cut the ring or band, as resultant loose threads may be a source of hemolysis, thrombosis, and/or thromboembolism.
- Intraoperative and/or postoperative echocardiography should be used to evaluate the effectiveness of the valve repair.

Minimizing regurgitation and systolic anterior motion (SAM) are important elements of an effective repair.
- Surgeons who use annuloplasty rings and bands should be current on all anticoagulation regimens.
- When postoperative anticoagulant therapy is used, the patient's anticoagulation status should be carefully monitored.
- Patients with intra-atrial thrombi or a giant left atrium may benefit from long-term anticoagulation therapy.
- The surgeon may desire that patients in atrial fibrillation remain on anticoagulation therapy until sinus rhythm is established.
- Do not alter or deform the ring or band to conform to annular anatomy as this could lead to ring/band fracture and possible mitral regurgitation.
- Do not squeeze the ring or band with sharp instruments as this may damage the surface of the stiffener, which may result in ring/band fracture and possible mitral regurgitation.
- The ring and band are indicated for use in the mitral position only. Use in the tricuspid position may result in ring/band fracture, conduction system damage, tricuspid regurgitation, and/or ring/band dehiscence.

5 PRECAUTIONS

- Do not use cutting edge needles, as they may damage the annuloplasty device potentially leading to ring/band dehiscence, ring/band fracture, and possible mitral regurgitation.

6 POTENTIAL ADVERSE EVENTS

While infrequent, certain complications have been reported when using annuloplasty ring/bands. These include the following:
- Uncorrected or recurrent regurgitation
- Stenosis
- Ring/Band dehiscence
- Hemolysis (even with mild regurgitation)
- Low cardiac output
- Heart block
- Systolic anterior motion (SAM) and left ventricular outflow tract obstruction (LVOTO)
- Damage to coronary arteries
- Endocarditis
- Thrombosis
- Thromboembolism
- Anticoagulant-related hemorrhage
- Ring/Band fracture
- Leaflet perforation

The potential for these complications should be considered when selecting the most beneficial surgical procedure for each patient.
To avoid or minimize occurrence of these adverse events, the annuloplasty repair, including sizing and implantation, should be conducted in accordance with the methods described in these Instructions for Use by surgeons with appropriate training and experience in valve repair.

7 INDIVIDUALIZATION OF TREATMENT

To allow for healing and incorporation of the annuloplasty ring or band by host tissue, regardless of cardiac rhythm, postoperative anticoagulation therapy should be considered for at least six weeks following surgery.

8 PATIENT COUNSELING INFORMATION

Patients with annuloplasty rings or bands who undergo dental or other potentially bacteremic procedures must be considered for prophylactic antibiotic therapy.

9 HOW SUPPLIED

9.1 Packaging

The CG Future® 638R Annuloplasty Ring is available in the following sizes for the mitral position: 24, 26, 28, 30, 32, 34, 36, and 38 mm. The CG Future® 638B Annuloplasty Band is available in the following sizes: 26, 28, 30, 32, 34, 36, and 38 mm.
The package contains a single annuloplasty ring or band assembly consisting of the device and holder (Figure 1) packaged in sterile, double-aseptic transfer pouches. The packaging system is designed to ease placement of the device into the sterile field. The ring and band assemblies are sterile if the pouches are undamaged and unopened. The outer surfaces of the outer pouch are NONSTERILE and must not be placed in the sterile field.

9.2 Storage

Store the product in its original packaging, including the outer shelf carton, in a clean, cool, and dry area to protect the product and minimize the potential for contamination.
The sterility and nonpyrogenicity of the CG Future® Annuloplasty Ring/Band are validated to remain unaffected until the Use By date identified on the shelf carton, provided the pouches are not opened or damaged.

10 DIRECTIONS FOR USE

10.1 Sizing

The CG Future® 7638 Ring/Band Sizer Set is used to select the proper CG Future® Annuloplasty Ring/Band size for repair of the mitral valve. Sizers are reusable; however, they must be cleaned and sterilized by autoclave (steam) prior to each use.
Proper ring/band size selection is an important part of valvular annuloplasty to help restore proper function. Use the CG Future® 7638 Annuloplasty Ring/Band Sizer Set and Medtronic 7615 Annuloplasty Handle for size selection.
The handle and sizers are provided NONSTERILE; they must be cleaned and sterilized prior to use. Align and insert the handle into the snap cavity of the sizer (Figure 2). The thin section of the handle is malleable, allowing the surgeon to align the sizers with the valve annulus.
Warning: Do not use other manufacturers' annuloplasty sizers or sizers from other Medtronic annuloplasty products to size the CG Future® Annuloplasty Ring/Band.
Mitral Valve
To determine the proper ring or band size, both the distance between the annular trigones and the area of the anterior leaflet must be measured. First, lower the sizer onto the valve annulus and align the sizer notches with the annular trigones. Second, gently extend the anterior (A) leaflet and cover its surface with the selected sizer. The sizer that has a notch spacing most nearly matching the intertrigonal distance (Figure 3) and a surface area most nearly matching that of the anterior leaflet corresponds to the size of the ring or band that should be selected.

10.2 Handling and Preparation Instructions

- Open the box and remove the product literature and Patient Registration Form.
- Remove the double-aseptic transfer pouch containing the device mounted to the holder.
- Inspect the pouches ensuring they have not been opened or damaged. The ring and band assemblies are sterile as long as the inner pouch has not been compromised. If the inner pouch is damaged, do not implant the device.
- If the outer pouch is damaged, the exterior surface of the inner pouch may not be sterile.
- Open the outer transfer pouch, and while still holding the bottom of the outer pouch, pass the inner pouch into the sterile field.
- The inner pouch should be opened only in the sterile field.

10.3 Device Implantation

The CG Future® Annuloplasty Ring/Band assembly may be used with or without the handle (Medtronic 7615 Annuloplasty Handle, provided separately).
Caution: The CG Future® Annuloplasty Ring/Band are designed for implantation only with interrupted-suture techniques.
Warning: The handle must be cleaned and sterilized prior to use.
To use the handle, align and engage the sterile handle into the snap fit cavity of the holder (Figure 4). The thin section of the handle is malleable, allowing the surgeon to align the device with the annulus.
Note: The handle must be inserted into the side of the holder with the snap fit cavity and the printed text.
Remove the serial number identification tag (Figure 5) and record the serial number in the patient's record. Verify that the serial number matches the serial number on the Patient Registration Form.
Warning: The serial tag must be removed from the ring/band for proper function. Do not cut or tear the ring/band fabric during removal of the serial tag.
Mitral Annulus Suture Placement
Place sutures in each trigone, approximately 4 mm in width.
Place additional interrupted sutures, approximately 4 mm in width, in the posterior portion of the mitral annulus following the line of cusp insertion (Figure 6). A total of approximately 10 to 14 sutures should be placed for the ring/band.
Warning: Avoid placing sutures in the circumflex coronary artery.
Note: Pledgets may be used for trigone sutures and mid-posterior annulus suture to reduce the possibility of ring/band dehiscence.
Band Suture Placement
Orient the band assembly on the mitral (M) annulus on the holder (Figure 7).
Pass sutures through the band, approximately 2 mm in width, entering at the bottom of the band and exiting the periphery of the band (Figure 8). The sutures placed in the trigonal tissue should be passed through the eyelets of the band stiffener (Figure 9).
Pass only one suture through the trigonal marker on the device.
Ring Suture Placement
Orient the ring assembly on the mitral (M) annulus on the holder (Figure 7).
Pass sutures through the ring, approximately 2 mm in width, entering at the bottom of the ring and exiting the periphery of the ring (Figure 8). Place sutures completely around the device, including the anterior mitral annulus region. The sutures placed in the trigonal tissue should be passed through the eyelets of the ring stiffener (Figure 9). Pass only one suture through the trigonal marker on the device.
Caution: The ring/band must be sutured through the eyelets into the trigonal tissue to ensure secure attachment.
Holder/Handle Removal
Use the holder/handle to push the ring or band down onto the valve annulus while pulling back on the sutures. Using a scalpel, cut the retention sutures on the holder in the areas indicated (Figure 10). Remove the disposable holder and handle from the valve annulus (Figure 11). Dispose of the holder.
Warning: Do not cut the ring or band fabric while cutting the holder retention sutures.
Knots, Testing
Tie all knots around the device securely (Figure 12), trim all excess sutures, and test valvular competency after removing the holder.
Warning: The CG Future® Annuloplasty Ring/Band holder must be removed from the device at the end of the procedure for proper function. Under no circumstances should the holder remain attached to the ring or band.
Warning: Suture knots must be securely tied. Loose knots and long suture tails may be a source of hemolysis, thrombosis, or thromboembolism.

10.4 Accessories

Use the CG Future® 7638 Annuloplasty Ring/Band Sizer Set to determine the appropriate device size. Refer to the CG Future® Annuloplasty Ring/Band Sizer Set Instructions for Use for detailed information on accessory use and sterilization.

Warning: Do not use other manufacturers' annuloplasty sizers or sizers from other Medtronic annuloplasty products to size the CG Future® Annuloplasty Ring/Band.
Use only the Medtronic 7615 Annuloplasty Handle to interface with the holder and sizers. Refer to the Medtronic Annuloplasty Handle Instructions for Use for detailed information on use and sterilization.

10.5 Sterilization

10.5.1 Ring/Band (Model 638R/638B)

The ring and band are provided sterile (ethylene oxide) on the holder and must not be resterilized. Rings and bands that have been damaged or contaminated from patient contact should not be used.

11 REGISTRATION INFORMATION

Note: Patient registration does not apply in countries where patient privacy laws conflict with providing patient information, including countries from the EU.
A patient registration form is included in each device package.
After implantation, please complete all requested information.
The serial number may be found on the package and on the identification tag attached to the device. Return the original form to the Medtronic address indicated on the form and provide the temporary identification card to the patient prior to discharge.

12 DISCLAIMER OF WARRANTIES

THE FOLLOWING DISCLAIMER OF WARRANTY APPLIES TO UNITED STATES CUSTOMERS ONLY:
The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of Warranty is held by any court of competent jurisdiction to be illegal, unenforceable, or in conflict with applicable law, the validity of the remaining portion of the Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.
DISCLAIMER OF WARRANTY
ALTHOUGH THE CG FUTURE® 638R/638B ANNULOPLASTY RING/BAND, THE CG FUTURE® 7638 RING/BAND SIZER SET, AND THE MEDTRONIC 7615 ANNULOPLASTY HANDLE, HEREAFTER REFERRED TO AS "PRODUCT," HAVE BEEN MANUFACTURED UNDER
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CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE, OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT, OR OTHERWISE.
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The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable, or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and all rights and

obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.

DISCLAIMER OF WARRANTY

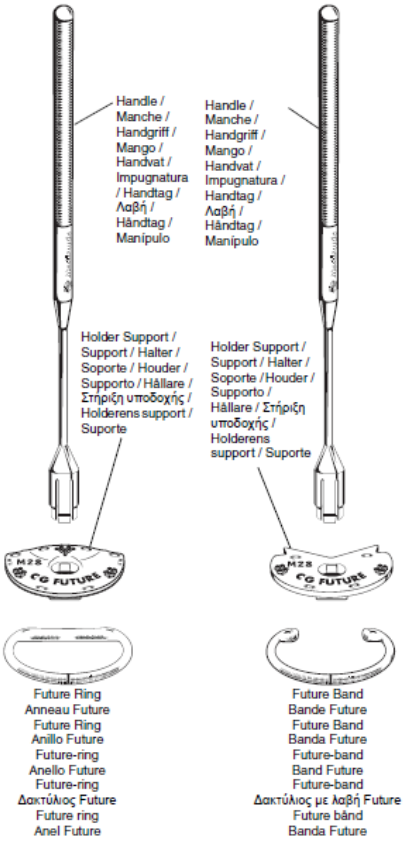
ALTHOUGH THE CG FUTURE® 638R/638B ANNULOPLASTY RING/BAND, THE CG FUTURE® 7638 RING/BAND SIZER SET, AND THE MEDTRONIC 7615 ANNULOPLASTY HANDLE, HEREAFTER REFERRED TO AS "PRODUCT," HAVE BEEN CAREFULLY DESIGNED,

MANUFACTURED, AND TESTED PRIOR TO SALE, THE PRODUCT MAY FAIL TO PERFORM ITS INTENDED FUNCTION SATISFACTORILY FOR A VARIETY OF REASONS. THE WARNINGS CONTAINED IN THE PRODUCT LABELING PROVIDE MORE DETAILED INFORMATION AND

ARE CONSIDERED AN INTEGRAL PART OF THIS DISCLAIMER OF WARRANTY. MEDTRONIC, THEREFORE, DISCLAIMS ALL WARRANTIES, BOTH EXPRESS AND IMPLIED, WITH RESPECT TO THE PRODUCT. MEDTRONIC SHALL NOT BE LIABLE FOR ANY INCIDENTAL OR

CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, OR FAILURE OF THE PRODUCT, WHETHER THE CLAIM IS BASED ON WARRANTY, CONTRACT, TORT, OR OTHERWISE.

Figure 1



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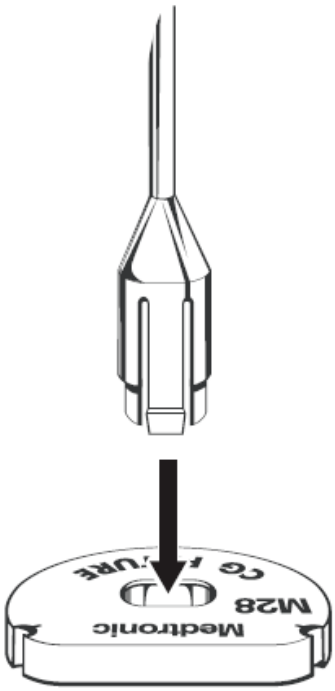

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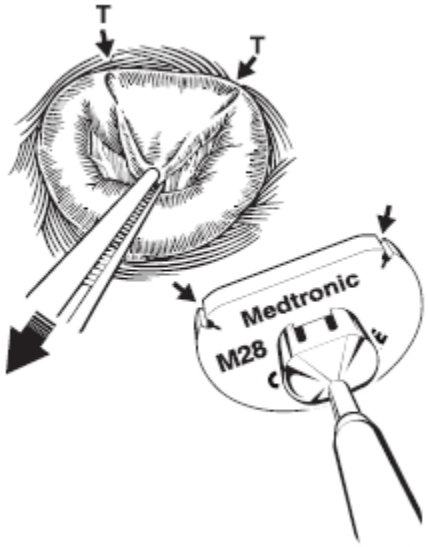

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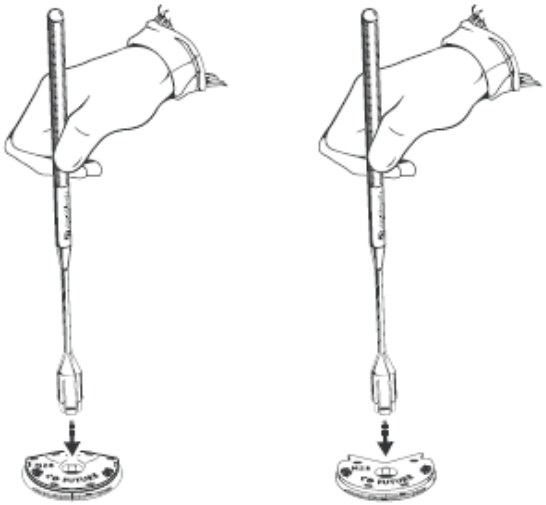

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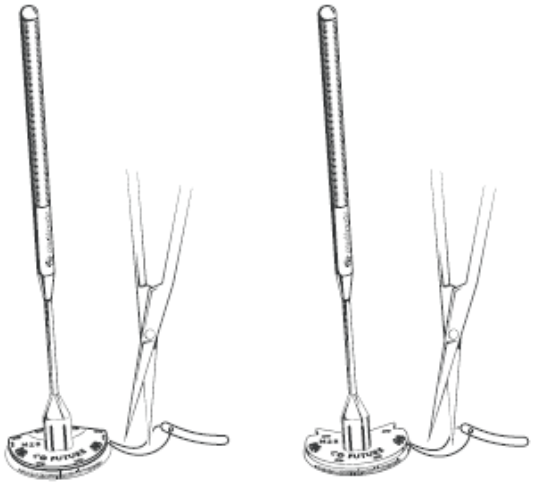

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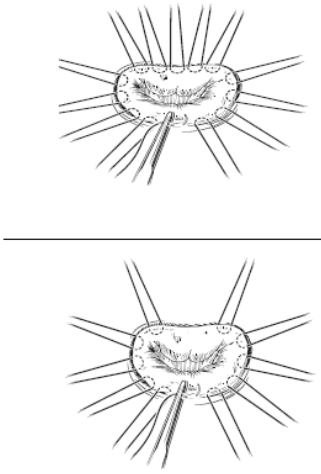

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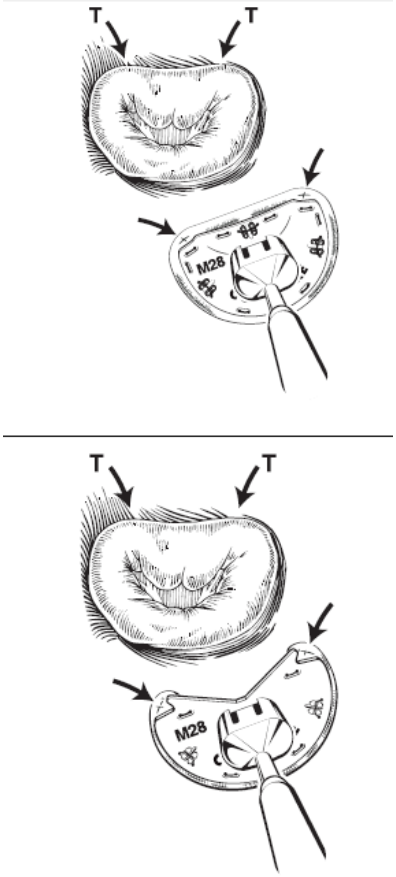

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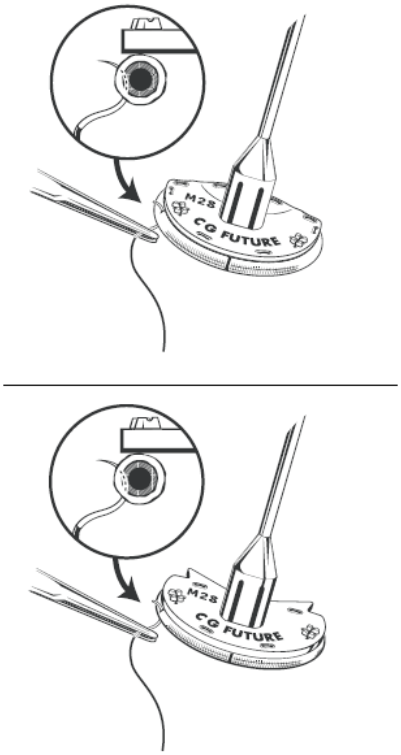

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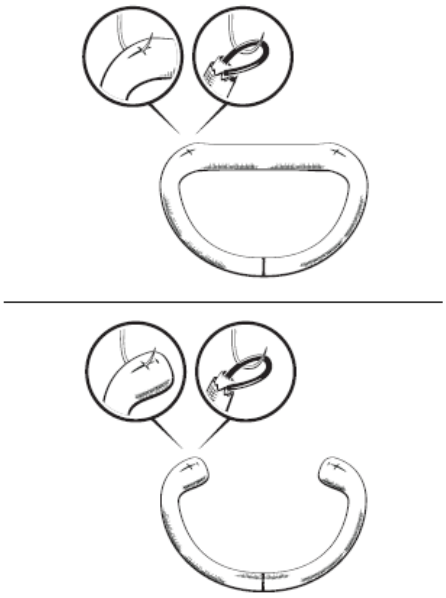

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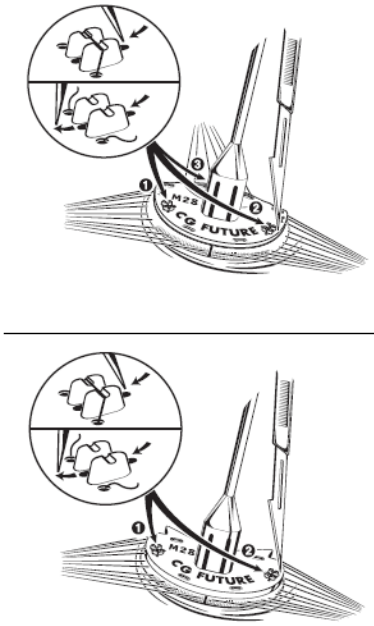

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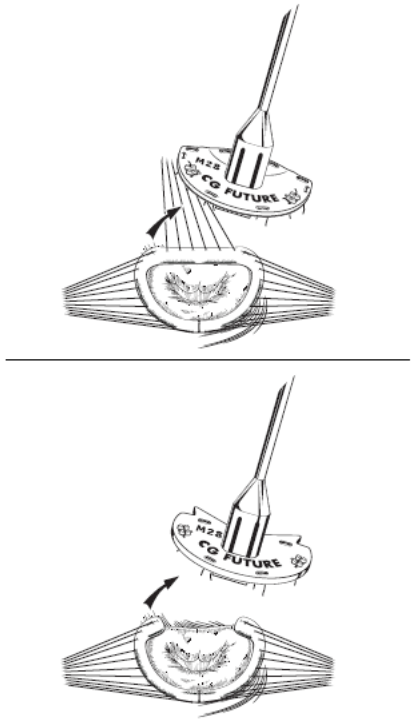

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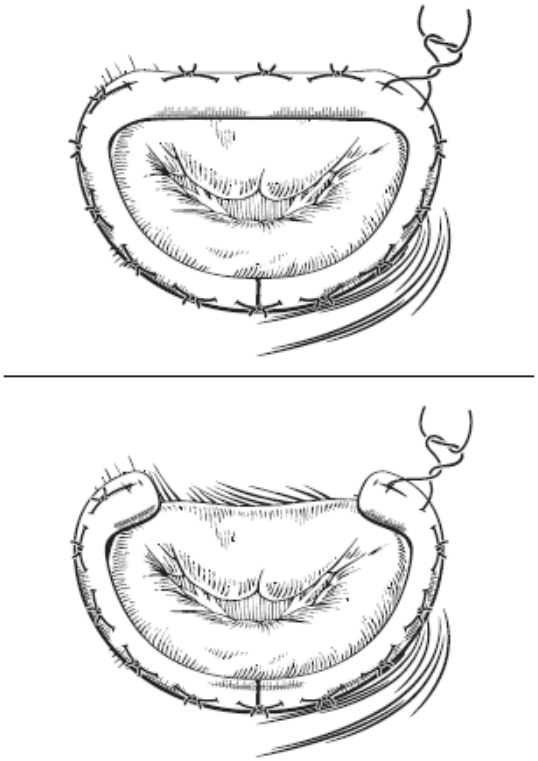

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Kritika Gupta, Clinical Study Manager Aditya Chachad, Clinical Study Manager

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	PRESERVE - MITRAL **P**rospective **RE**gistry to **S**tudy Clinical Outcom**E**s of **R**epair of Mitral **V**alv**E**s in South Asia.
Clinical Investigation Plan Identifier	MDT16016SUR002
Clinical Investigation Plan Version	Version 1.0, dated 10-APR-2017
Sponsor/Local Sponsor	Medtronic plc. Clinical Research Mailstop: MVS66 Mounds View South 8200 Coral Sea St. NE Mounds View, MN 55112 **Regional Sponsor**: Vinay Rajan, Ph.D India- Medtronic Pvt. Ltd. Solitaire Corporate Park, Bldg No. 12, 4th Floor, Andheri -Ghatkopar Link Road, Andheri-East Mumbai, Maharashtra 400 093 INDIA Contact Number: +91-22-33074700
Document Version	Version 2.0, dated 09-AUG-2019

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Shuzhen Li, Principal Statistician
2.0	• Revised analysis set for primary and secondary endpoints to Successfully Implanted subjects. • Revised analysis method for new onset of atrial fibrillation to Kaplan-Meier analysis. • Added specification on the time point at which a subject is deemed to have an attempted implant. • Added specification on the standard error estimator for the Kaplan-Meier analyses. • Last follow-up date definition was revised for subjects with exit reason of lost to follow-up. • Revised Section 7.6 to include Enrolled and Successfully Implanted cohorts in reporting of demographic and other baseline characteristics. • Revised Section 7.7 to include Attempted Implant and Successfully Implanted cohorts in reporting of procedural characteristics. • Added subgroup analyses for the primary and selected secondary endpoints.	Angie Zhang, Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACC	American College of Cardiology
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Hospital Association
ASE	American Society of Echocardiography
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSH	Medtronic Coronary and Structural Heart
CVD	Cardiovascular Disease
ECG	Electrocardiogram/Electrocardiography
eCRF	Electronic Case Report Form
IFU	Instructions For Use
LAR	Legally Authorized Representative
MR	Mitral Regurgitation
NYHA	New York Heart Association
PRESERVE – MITRAL	Prospective REgistry to Study Clinical OutcomEs of Repair of Mitral ValvEs in South Asia
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect

3. Introduction

Cardiovascular Diseases (CVD) are the leading cause of mortality in India, contributing to 25% of all mortality in the country. The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 100,000 population in India is higher than the global average of 235 per 100,000 population [1].

One of the important pathologies seen in patients with cardiovascular disease is mitral valve regurgitation and insufficiency. Patients might suffer from different types of mitral valve dysfunction leading to different levels of regurgitation.

Mitral valve repair is established as a procedure to alleviate mitral valvular insufficiency/stenosis. The pathophysiology of mitral valve insufficiency can be ischemic, rheumatic, degenerative, congenital, infective, myxomatous, etc.

Mitral valve repair may lead to better outcomes as compared to replacement. Western studies on mitral valve repair have typically focused on patients with ischemic pathophysiology. Current ACC/AHA guidelines [2] state that mitral valve repair is recommended in preference to mitral valve replacement in certain patients with chronic severe primary MR limited to posterior leaflet, or involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished. Concomitant repair is indicated for patients with chronic severe primary MR if they undergo cardiac surgery.

Despite the guidelines, there may be local and regional differences in the standard practice in different geographies. While there are some Indian studies that have looked into mitral valve repair [3], [4], [5], there is still a need to gather more local evidence on clinical outcomes at long term follow up (12 months). The significant proportion of mitral valve repair patients in India have rheumatic disease. Mitral valve repair is more technically challenging in this population, and is associated with higher failure rate.

Given this background, it is clear that the significant body of evidence for mitral valve annuloplasty from the west may not give a realistic picture of patients undergoing the same procedure in South Asia. Due to the difference in disease pathophysiology, the significant population of patients with rheumatic disease and differing surgical practice, there is a need to conduct a geography-specific study to understand the clinical outcome of patients undergoing mitral valve annuloplasty in the region. PRESERVE-Mitral, a prospective registry to study long term performance of annuloplasty systems is thus proposed to document clinical outcomes, physician practice and report on outcomes in these patients.

There is limited local evidence on mitral repair products in South Asia and a prospective post-market registry will provide real world data on clinical outcomes.

4. Study Objectives

4.1 Primary Objective(s)

The objective of this registry is to gather data on the clinical outcomes of Medtronic mitral repair products (Profile 3D™ or CG Future® Annuloplasty systems, which include Profile 3D Ring, CG Future Ring and CG Future Band) in the approved intended use up to 12 months from the day of procedure.

4.2 Secondary Objective(s)

Characterize the demographics of the patients undergoing mitral valve repair using annuloplasty systems in South Asia, and assess the functional and procedural outcomes of the procedure.

5. Investigation Plan

5.1 Study Design

PRESERVE-Mitral is a prospective non-randomized non-interventional post-market registry. A total of 200 patients who are eligible and who are intended to be implanted with a Profile 3D™ or CG Future® Annuloplasty system in the surgical repair procedure will be included in the study.

The subjects will be evaluated at discharge for evaluation of procedural success and subsequently followed up as per standard-of-care at the site from 3-6 months (90 days to 210 days) post procedure and at 12 months (365 days +/- 30 days) post procedure for assessment of longer-term outcome at which time subjects will also exit the study. Echo images will be evaluated pre-implant, intra-op, discharge and during follow ups, according to the standard routine in the center.

5.2 Selection of Subjects

5.2.1 Study Population

The patient population includes all patients suffering from mitral valve disease, indicated for a mitral valve repair procedure, either as a stand-alone procedure or concomitant to another procedure (for example, coronary artery bypass grafting, tricuspid valve repair, treatment of atrial fibrillation, etc. but excluding patients undergoing aortic valve replacement) and for which the surgeon considers the implantation of a Profile 3D™ or CG Future® Annuloplasty system most appropriate to reconstruct the regurgitant valve.

5.2.2 Subject Enrollment

A subject is considered enrolled in this study at the time at which he/she signed the Patient Informed Consent Form.

5.2.3 Inclusion Criteria

1. Patients with valvular insufficiency and/or stenosis and indicated for the reconstruction and/or remodeling of pathological mitral valves with Profile 3D™ or CG Future® Annuloplasty systems.
2. Indications and contraindications provided in the product Instructions for Use (IFU).
3. Subject is 18 years of age or older.
4. The patient or his/her Legally Authorized Representative (LAR) has been informed about the nature of the registry and the patient informed consent for study participation has been obtained prior to performing any study-related procedures from the subject or LAR, as per applicable local requirements.

5.2.4 Exclusion Criteria

1. Contraindications as per IFU:
   a. Heavily calcified valves;
   b. Valvular retraction with severely reduced mobility;
   c. Active bacterial endocarditis.
2. Aortic valve replacement as concomitant procedure.
3. Already participating in another clinical study, possibly leading to bias and jeopardizing the scientific appropriate assessment of the study endpoints.

6. Determination of Sample Size

The sample size of 200 subjects who are eligible and intended to be implanted with a Profile 3D™ or CG Future® Annuloplasty system in the surgical repair procedure is adequate and appropriate for the evaluation of local evidence and obtaining real world data on clinical outcomes following implantation of these two products. This sample size was not statistically derived as this is not a hypothesis driven study.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized, including the number of subjects enrolled, attempted implant, successfully implanted, died, explanted, withdrawn, lost to follow-up, and completed each visit during the study.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol violations (study deviations) will be reported to Medtronic throughout the study by each site and identified through monitoring activities. CIP deviations will be summarized.

7.1.3 Analysis Sets

There are three analysis sets defined for this study. Analysis sets used for each objective are defined in the corresponding objective section. The primary analysis set is the Successfully Implanted analysis set.

- Enrolled analysis set: Composed of all subjects who signed the Patient Informed Consent Form. Time zero begins on the date of informed consent.
- Attempted Implant analysis set (AT): Composed of all enrolled subjects who were attempted for a Profile 3D™ or CG Future® Annuloplasty system implantation. A subject with one or more attempts of the Medtronic study device recorded on the procedure case report form (CRF) is considered as implant attempted. Time zero begins on the date of the first attempted procedure.
- Successfully Implanted analysis set (IMP): Composed of all AT subjects who had either a Profile 3D™ or CG Future® Annuloplasty system implanted successfully. Time zero begins on the date of implant procedure.

All data collected from enrolled, attempted implant, and successfully implanted subjects will be utilized in the analyses as appropriate. Analyses of the primary and secondary endpoints will be descriptive, and no statistical hypothesis tests will be performed.

7.2 General Methodology

Descriptive statistics will be used to report study data. For continuous variables (e.g. age), the mean, median, standard deviation, minimum, maximum, and first and third quartiles will be presented. For categorical variables, the number and percentage of subjects in the category of interest will be presented. For time to event data, Kaplan-Meier analyses of event or event-free rates at discharge, 6 and 12 months will be presented. For these analyses, the time points will correspond to 7 days, 183 days and 365 days post implantation respectively. At each time point with data, the product limit estimate of the event or event-free rates, and the loglog transformed 95% confidence interval using the Peto standard error will be presented. For subjects without an event, the date of censoring will be the latest date of all follow-up visits (including phone and/or mail correspondence), assessments, events (including death) and study exits. For subjects whose exit reason is lost to follow-up, the last follow-up date will be the latest date of the follow-up visits (including phone and/or mail correspondence), assessments and events.

7.3 Center Pooling

Although data for this registry will be collected from multiple centers, no center pooling analyses are planned.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing, unused and spurious data and dropouts. Unless otherwise specified, no statistical techniques will be used to impute missing data. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year. These resolutions of partial dates are subject to the restrictions that events must occur no earlier than the procedure date or after study exit.

7.5 Adjustments for Multiple Comparisons

No multiple comparisons/multiplicity adjustments will be made.

7.6 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Enrolled and Successfully Implanted analysis sets. Continuous variables will be summarized with means, medians, standard deviations, minimums, maximums, and first and third quartiles. Categorical variables will be summarized with frequencies and percentages.

7.7 Treatment Characteristics

Procedural data will be summarized for the Attempted Implant and Successfully Implanted analysis sets. Continuous variables will be summarized with means, medians, standard deviations, minimums, maximums, and first and third quartiles. Categorical variables will be summarized with frequencies and percentages.

7.8 Interim Analyses

An interim summary of the data is planned when all enrolled and successfully implanted subjects have had the opportunity to be followed through the discharge visit. This is an observational study. No statistical hypothesis tests will be performed, and there are no pass/fail criteria for the results of this study.

7.9 Evaluation of Objectives

7.9.1 Primary Endpoint #1

Improvement in mitral valve regurgitation (MR) (grade) at 12 months post procedure.

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Mitral valve function will be based on site echocardiographic recordings. The parameter to be estimated is the grade of mitral valve regurgitation using echo, in subjects at baseline and 12 months post procedure. The grades of MR, 0-4, will correspond to the ASE guidelines (as described in Table 1 in CIP) ranging from no MR, Mild MR, Moderate MR, Moderate-to-Severe MR and Severe MR.

Data Collection and Analysis Dataset:
Data will be collected on an ECHOCARDIOGRAM (CV) CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort, and for the IMP subjects with CG Future Band, CG Future Ring and Profile 3D Ring respectively. IMP subjects having available MR collection at both baseline and 12 months post procedure will be included in the analysis.

Analysis Method:
For each subject with paired data, the change from baseline (improved, no change, worsened) will be evaluated at 12 months. This primary endpoint of improvement in MR (grade) will be presented with frequencies and percentages of subjects with improved MR at 12 months. Two-sided 95% exact binomial confidence intervals of the percent of subjects overall and in each of the three subgroups with improved MR at 12 months will also be reported.

7.9.2 Primary Endpoint #2

All-cause mortality rate at 12 months post procedure.

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
All-cause mortality event rate estimate will be provided at 12 months post procedure.

Data Collection and Analysis Dataset:
Data will be collected on an AE CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort, and for the IMP subjects with CG Future Band, CG Future Ring and Profile 3D Ring respectively.

Analysis Method:
A Kaplan-Meier analysis will be performed.

7.9.3 Secondary Endpoint #1

Characterization of subject demographics and pathophysiology of mitral valve disease.

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Baseline demographics and clinical variables will be summarized. The following subject characteristics at baseline will be reported: age (in years), gender, previous cardiovascular surgery, symptoms of heart failure, cardiac rhythm, New York Heart Association (NYHA) classification, risk factors, level of regurgitation, type of mitral valve deficiency, etc.

Data Collection and Analysis Dataset:
Data will be collected on a DEMOGRAPHICS (DM) or PRE-OPERATIVE CLINICAL HISTORY (MH) CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort.

Analysis Method:
Descriptive statistics will be provided. For continuous variables (e.g. age), the mean, median, standard deviation, minimum, maximum, and first and third quartiles will be presented. For categorical variables, the number and percentage of subjects in the category of interest will be presented, as described in section 7.2.

7.9.4 Secondary Endpoint #2

Improvement in mitral valve regurgitation (MR) (grade) at discharge and first follow up (3-6 months).

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Mitral valve function will be based on site echocardiographic recordings. The parameter to be estimated is the grade of mitral valve regurgitation using echo, in subjects at discharge and 3-6 months post procedure. The grades of MR, 0-4, will correspond to the ASE guidelines (as described in Table 1 in CIP) ranging from no MR, Mild MR, Moderate MR, Moderate-to-Severe MR and Severe MR.

Data Collection and Analysis Dataset:
Data will be collected on an ECHOCARDIOGRAM (CV) CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort, and for the IMP subjects with CG Future Band, CG Future Ring and Profile 3D Ring respectively. IMP subjects having available MR collection at baseline, discharge and 3-6 months post procedure will be included in the analysis.

Analysis Method:
For each subject with paired data, the change from baseline (improved, no change, worsened) will be evaluated at discharge and 3-6 months follow up. This secondary endpoint of improvement in MR (grade) will be presented with frequencies and percentages of subjects with improved MR at discharge and 3-6 months. Two-sided 95% exact binomial confidence intervals of the percent of subjects overall and in each of the three subgroups with improved MR at discharge and 3-6 months will also be reported.

7.9.5 Secondary Endpoint #3

Improvement in New York Heart Association (NYHA) functional class at discharge, first follow up (3-6 months) and second follow up (12 months) compared to baseline.

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

The parameter to be estimated is NYHA classification at discharge, 3-6 months and 12 months follow-up.

New York Heart Association (NYHA) classification and risk factors are defined as below:

Classification	Description
Class I	Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Data Collection and Analysis Dataset:

Data will be collected on a DEMOGRAPHICS (DM) or DISCHARGE/FOLLOW UP (SV) CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort. All IMP subjects with available NYHA collections (I/II/III/IV) or died at baseline, discharge, 3-6 months and 12 months follow up visits will be included in the analysis.

Analysis Method:

For each subject with paired data or who died prior to a visit, the change from baseline (improved, no change, worsened or died) will be calculated at discharge, 3-6 months, and 12 months. The endpoint of improvement in NYHA class will be presented with frequencies and percentages of subjects with improved NYHA at discharge, 3-6 months, and 12 months. The two-sided 95% exact binomial confidence interval of the overall percent of subjects with improved NYHA class at discharge, 3-6 months, and 12 months will also be reported.

7.9.6 Secondary Endpoint #4

Hospitalization for Heart Failure at 6 and 12 months post procedure.

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Hospitalization for Heart Failure event rate estimate will be provided at 6 and 12 months post procedure.

Data Collection and Analysis Dataset:
Data will be collected on an AE CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort.

Analysis Method:
A Kaplan-Meier analysis will be performed.

7.9.7 Secondary Endpoint #5

Mitral valve re-intervention at discharge, 6 and 12 months post procedure.

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Mitral valve re-intervention event rate estimate will be provided at discharge, 6 and 12 months post procedure.

Data Collection and Analysis Dataset:
Data will be collected on a RE-INTERVENTION (RE-OP) CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort.

Analysis Method:
A Kaplan-Meier analysis will be performed.
The number and percentage of subjects with mitral valve re-intervention post implant on or prior to discharge will also be presented, as described in section 7.2.

7.9.8 Secondary Endpoint #6

Stroke at 6 and 12 months post procedure.

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Stroke event rate estimate will be provided at 6 and 12 months post procedure.

Data Collection and Analysis Dataset:
Data will be collected on an AE CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort.

Analysis Method:
A Kaplan-Meier analysis will be performed.

7.9.9 Secondary Endpoint #7

New onset of atrial fibrillation (AF), as evaluated through follow up ECG at discharge, first follow up (3-6 months) and at second follow up (12 months), as well as on the AE form.

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
New onset of AF is defined as when the subject did not present with prior history of AF at baseline nor was AF detected at baseline visit, but AF did manifest post procedure and was either diagnosed during the study visits (discharge, 3-6 months or 12 months visit) or was otherwise diagnosed during the duration of subject participation in the study.

Data Collection and Analysis Dataset:
Data will be collected on a DISCHARGE/FOLLOW UP (SV) CRF or an AE CRF.
This objective will be analyzed for the Successfully Implanted (IMP) cohort.

Analysis Method:
A Kaplan-Meier analysis will be performed.

7.9.10 Secondary Endpoint #8

Number of attempts required for procedural success, and bypass time as a measure of procedural complexity, as measured by standard operating room procedures at the site.

Hypothesis/Decision criteria:
No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:
Number of attempts required for procedural success, and bypass time as a measure of procedural complexity.

Data Collection and Analysis Dataset:
Data will be collected on an IMPLANT (IMP) CRF.

This objective will be analyzed for the Successfully Implant (IMP) cohort.

Analysis Method:
The number of attempts (per subject) required for procedural success and the bypass time will be summarized. Descriptive statistics will be provided.

7.10 Safety Evaluation

Primary and secondary safety endpoints will be summarized as noted in Section 7.9 of this Statistical Analysis Plan (SAP). Adverse events will be provided in a listing for all attempted implant subjects. The proportion of subjects experiencing events will also be summarized by MEDDRA coding (System Organ Class and High Level Term) for successfully implanted and attempted but not successfully implanted subjects.

7.11 Health Outcomes Analyses

No health outcomes analyses are planned.

7.12 Changes to Planned Analysis

Analysis set defined in the CIP for the primary and secondary endpoints is changed to the Successfully Implanted set in order to align with other surgical valve studies.

New onset of atrial fibrillation will be evaluated using Kaplan-Meier method instead of percent of subjects as described in the CIP in order to incorporate subject censoring in the course of the study. Atrial fibrillation identified on the post-procedural ECG or AE forms will be included in the analysis.

Changes to V1.0 of the SAP include: Baseline data will be presented for the Enrolled and Successfully Implanted cohorts, and procedural data will be presented for the Attempted Implant and Successfully Implanted cohorts. As one of the objectives of the registry is to characterize subjects who are considered eligible for mitral valve repair in South Asia, analyzing baseline and procedural characteristics on these analysis cohorts will cover the populations of interest.

Sub-group analyses will be performed on the Successfully Implanted subjects with CG Future Band, CG Future Ring and Profile 3D Ring respectively for the primary and selected secondary endpoints.

8. Validation Requirements

Level 1 validation (independent validation) will be used for the analysis datasets and the primary and secondary endpoints. Level 2 validation (peer review) will be used for additional analyses, data summaries, and listings.

9. References

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10. Statistical Appendices

There are no statistical appendices for this study.