PMCF for the Harpoon Medical Device

Assessment of the safety and performanCe of thE HARPOON™ Beating Heart Mitral Valve Repair System; a multi-center post-market stuDy (ASCEND #2018-22)

NCT04382612

November 25, 2019

Assessment of the safety and performanCe of thE HARPOON™ Beating Heart Mitral Valve Repair System; a multi-center post-market stuDy (ASCEND)

CLINICAL STUDY PROTOCOL

Protocol Number: 2018-22

Version: B
25 November 2019

Study Sponsor:
HARPOON Medical, an indirect wholly-owned subsidiary of Edwards Lifesciences Corporation
Edwards Lifesciences
One Edwards Way
Irvine, CA 92614
USA

1.0 PROTOCOL REVISION HISTORY

Protocol Revision Number	Protocol Revision Date
A	13 September 2019
B	25 November 2019

2.0 PROTOCOL SIGNATURE PAGE

Study Title:	**ASsessment of the safety and performanCe of thE HARPOON™ Beating Heart Mitral Valve Repair System; a multi-center post-market stuDy (ASCEND)**
Protocol Number:	**2018-22**
Version:	**Rev. B**
Date:	**25 November 2019**

I have read this protocol and agree to participate in the clinical investigation sponsored by HARPOON Medical, an indirect wholly-owned subsidiary of Edwards Lifesciences Corporation. I agree to conduct this investigation according to the requirements of the study protocol and in accordance with the International Standard ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, applicable European or regional laws and regulations, and conditions imposed by the reviewing Ethics Committee.

I agree to supervise all sub-investigators at my site as well and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study. This protocol contains confidential proprietary information with respect to Edwards Lifesciences' products and clinical studies. I agree to hold this information in confidence and not to disclose it to any third parties as outlined in the clinical trial agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose is entered into by the parties.

STATEMENT OF COMPLIANCE

The Study Protocol will be conducted in accordance with

- Declaration of Helsinki (Rev. 2013)
- ISO 14155: 2011

In addition, the Study Protocol will comply with any applicable regional regulations. The clinical investigation shall not begin until the required approval/favourable opinion from the EC is obtained.

INVESTIGATOR SIGNATURE	DATE
INVESTIGATOR NAME (PRINTED)	

3.0 STUDY CONTACTS

3.1 SPONSOR AND STUDY CONTACTS

STUDY DIRECTOR	PROJECT MANAGER

EUROPEAN AUTHORIZED REPRESENTATIVE	PRINCIPAL INVESTIGATOR
Edwards Lifesciences Services GmbH Edisonstrasse 6 D-85716 Unterschleisseheim Germany Tel: +49 89 95475-0	

3.2 STUDY OVERSIGHT

ECHO CORE LABORATORY	CLINICAL EVENTS COMMITTEE

CLINICAL RESEARCH ORGANIZATION

3.3 CLINICAL SITES

The study will be conducted in the following European countries: Austria, Germany, Italy, Poland, Switzerland and United Kingdom. The Sponsor will maintain a list of principal investigators and investigational sites for the duration of the study; the definitive list of sites will be provided with the final clinical investigation report of the study.

4.0 PROTOCOL SYNOPSIS

Title:	**AS**sessment of the safety and performan**C**e of th**E** HARPOO**N**™ Beating Heart Mitral Valve Repair System; a multicenter post-market stu**D**y (ASCEND)
Protocol Number:	2018-22
Sponsor	HARPOON Medical, an indirect wholly-owned subsidiary of Edwards Lifesciences Corporation
Design:	A single arm, prospective, multicentre, non-randomised and open-label post-market study
Device:	HARPOON™ Beating Heart Mitral Valve Repair System (MVRS)
Population:	Patients with severe degenerative mitral regurgitation as a result of mid-segment posterior leaflet prolapse undergoing treatment with HARPOON™ Beating Heart Mitral Valve Repair System
Enrolment:	250 implanted subjects in up to 25 centers in Europe
Duration:	Initial enrolment: Q4 2019 Last enrolment: Q4 2021 Last follow-up visit: Q1 2027
Follow-up:	Follow-up at 7 days or discharge from hospital post-index procedure (whichever occurs first), at 30 days, and at 6, 12, 18, 24, 36, 48, and 60 months post-treatment
Objectives:	To evaluate the long-term safety and performance of the HARPOON™ MVRS for use in patients presenting with severe degenerative mitral regurgitation due to posterior leaflet prolapse in the post-market phase.
Endpoints:	**Primary Safety Endpoint:** ➢ Freedom from all-cause mortality, disabling stroke and life- threatening bleeding at 30 days post-implant. **Primary Performance Endpoint**: ➢ Procedure success at 30 days post-treatment, as measured by: Technical success with reduction of MR to less than or equal to mild and the absence of major device or procedure-related SAEs.
Other Planned Analyses:	➢ Technical success defined as survival and exit from the operating room (OR) with successful implantation of 3 or more expanded polytetrafluoroethylene (ePTFE) chords. ➢ Freedom from major device or procedure-related serious adverse event (SAE) at 30 days, 1 year and 2 years post-implant ➢ Quality of Life (change from baseline to 1 and 6 months)

- 6-minute walk test (change from baseline to 1 and 6 months)
- Freedom from ePTFE chord rupture as reported by echo core lab at 1 year and 2 years post-implant
- Freedom from reoperation or re-intervention due to ePTFE chord rupture at 1 year and 2 years post-implant
- Functional improvement from baseline NYHA Functional Classification at 1 year and 2 years post-implant
- Freedom from reoperation or reintervention on the mitral valve annually through 5 years post-implant
- Freedom from ≥ moderate MR annually through 5 years post-implant

Subject Enrolment:

Inclusion Criteria:

Each subject is required to meet all of the following inclusion criteria:

1. Subject is ≥ 18 years old
2. Presence of severe MR as read on a transthoracic echocardiographic study
3. Mitral leaflet coaptation surface is sufficient to reduce mitral regurgitation without undue leaflet tension (approximate leaflet to gap ratio of 2:1) based on the judgment of the patient eligibility committee and the operating surgeon
4. Degenerative mitral valve disease with mid-segment P2 prolapse
5. Patient is able to sign informed consent and able to return for follow-up and is capable of participating in all testing associated with this clinical investigation

Exclusion Criteria:

A subject meeting any of the following criteria shall be excluded:

1. Patient is of the age where further growth is expected
2. Active endocarditis
3. Left ventricular or left atrial appendage thrombus
4. Severe mitral annular and/or leaflet calcification
5. Cannot tolerate procedural anticoagulation or post-procedure antiplatelet regimen
6. Mitral stenosis
7. Functional Mitral Valve disease
8. Previous mitral valve replacement surgery
9. Fragile or thinning apex
10. Contraindications to transoesophageal echocardiography (atlantoaxial disease, severe generalized cervical arthritis, upper gastrointestinal bleeding, significant dysphagia and odynophagia, has received extensive radiation to the mediastinum)
11. Patient is pregnant or lactating

Statistical Analysis: The primary safety and performance endpoints will be summarized by counts, percentages and corresponding 95% confidence intervals. Other categorical variables will be summarized by counts and percentages. Continuous variables

will be summarized using means, medians, ranges and standard deviations.

Statistical calculations will be based on all available data. No missing value imputations are planned for primary safety and effectiveness endpoints. Missing month and days for adverse events will be imputed. An initial analysis of apparent product failure will be conducted once 50 patients achieve 12 months of follow-up. Thereafter, a failure analysis will be repeated for each subsequent 10 patients achieving 12 months of follow-up. The rates of apparent product failure will be deemed unacceptable if the lower limit of any 95% confidence interval at 12 months is above 6%.

Study Oversight:

Echo Core Lab will evaluate all echocardiograms performed per protocol. (Echocardiograms will be obtained at Baseline, Discharge, 30 days, 6, 12, 18, 24, 36, 48 and 60 months).

Clinical Events Committee will adjudicate all potential safety endpoints (death, stroke, bleeding) and reintervention post-index procedure through the 2-year follow up.

Safety Review will be conducted for all adverse events reported during the course of the study.

Routine Monitoring will be conducted for reported data per the monitoring plan.

5.0 ABBREVIATIONS

AE	Adverse event
CA	Competent authority
CE	Conformité Européene
CEC	Clinical events committee
CKD	Chronic kidney disease
CRF	Case report form
EC	Ethics Committee
ECL	Echo Core Laboratory
EDC	Electronic data capture
eCRF	Electronic case report form
ePTFE	Expanded polytetrafluoroethylene
GCP	Good clinical practice
ID	Identity Number
ISO	International Organization for Standardization
LTFU	Lost to follow-up
MDD	Medical Device Directive
MR	Mitral Regurgitation
MVRS	Beating Heart Mitral Valve Repair System
NYHA	New York Heart Association
OR	Operating Room
PA	Pulmonary Artery
PEC	Patient Eligibility Committee
SAE	Serious Adverse Event
SOC	Standard of Care
TOE	Transoesophageal Echocardiogram
TTE	Transthoracic Echocardiogram
USADE	Unanticipated Serious Adverse Device Effect

Table of Contents

List of Tables

Attachments

6.0 INTRODUCTION AND BACKGROUND

6.1 MITRAL REGURGITATION, TRANS-APICAL VALVE REPAIR, AND THE HARPOON™ MVRS

Mitral valve disease is the second most common valvular heart disorder requiring surgery in Europe, with nearly 8 million Europeans estimated to have severe mitral valve regurgitation (MR) (AGENAS, 2015). MR results in a volume overload on the left ventricle which in turn leads to ventricular dilation, decreased ejection performance, pulmonary hypertension, symptomatic congestive heart failure, atrial fibrillation, right ventricular dysfunction and death. Successful surgical mitral valve repair restores mitral valve function, eliminates volume overload on the left ventricle, improves symptom status and prevents adverse left ventricular remodelling.

The large majority of MR results from either degenerative disease (caused by elongated or ruptured native chords that fail to support the mitral valve leaflets) or functional ischemic or idiopathic MR (the motion of the normal mitral valve leaflets is restricted by the enlarged ventricle) both of which lead to ineffective valve closure and regurgitation. Other less common causes of chronic primary MR include infective endocarditis, connective tissue disorders, rheumatic heart disease, cleft mitral valve, and radiation heart disease. If the subsequent volume overload of chronic primary MR is prolonged and severe, it causes myocardial damage, heart failure (HF), and eventual death. Correction of the MR is curative (Nishimura *et al.,* 2014).

There is no effective medical treatment for degenerative MR (DMR). Medical treatment, e.g. diuretics, vasodilators, might relieve HF symptoms but does not alter the course of DMR and ultimately surgery will be required (Nishimura et al., 2016). Two-thirds of all mitral valve surgical procedures in North America are performed on patients with degenerative MR and that percentage is estimated to be similar in Europe. Open cardiac surgery is a common method of treating DMR which involves replacing and/or supplementing elongated or ruptured chords with artificial chords made of ePTFE, a commercially available material which has a 20+ year history of safety in conventional mitral valve repair procedures.

Current ESC/EACTS Guidelines state that surgery is indicated in:

- asymptomatic patients with LVEF ≤60% or LVESD ≥45mm, new onset AF or SPAP >50mmHg and who are at low surgical risk;
- symptomatic MR patients with LVEF >30% or those who are refractory to medical treatment and in whom a durable valve repair is likely with low comorbidity.

In all patients, valve repair rather than valve replacement is advocated whenever possible and is now the standard of care (Vahanian et al. 2012). A systematic review found that mortality is particularly high in patients >80 years old: 10% for MV replacement (N=3,105) compared with 7% for MV repair (N=2,642), with 5-year survival rates of 23% for MV replacement (N=335) and 29% for MV repair (N=250). It was concluded that many patients are unfit for major heart surgery (Andalib et al. 2014).

Although open-heart surgery is the gold-standard approach for the treatment of severe MR, it is not performed in up to 50% of patients due to the increased risk associated with co-morbidities. Excellent outcomes can be achieved in most patients with minimally invasive approaches and transcatheter mitral interventions might be an alternative therapeutic option (Maisano *et al.* 2015; Lam *et al.* 2011).

Mitral valve repair technologies, including the HARPOON™ Beating Heart MVRS (Chordal repair), can be used in cases of DMR. The following available treatments to replace ruptured or elongated chordae tendinae can reduce MR. However, other than the HARPOON™ Beating Heart Mitral Valve Repair System, there is no currently effective medical therapy that treats or cures MR.

- **Edge-to-edge leaflet repair:** MitraClip (Abbott Vascular); Cardica Mitral Repair (Cardica); MitraFlex (TransCardiac); PASCAL (Edwards Lifesciences)
- **Chordal repair:** *ePTFE sutures, HARPOON™ MVRS (HARPOON Medical),* NeoChord DS1000 (NeoChord); V-Chordal-Off Pump (Valtech); V-Chordal-Transfemoral (Valtech); MISTRAL (Mitralix)
- **Indirect annuloplasty:** CARILLON (Cardiac Dimensions) (Lam *et al.* 2011).
- **Direct annuloplasty:** GDS Accucinch (GDS); Mitralign Bident (Mitralign); Cardioband TF (Valtech); Millipede Ring (Millipede); Kardium MR (Kardium); ValCare MV Repair (ValCare), QuantumCor (QuantumCor)
- **Enhanced coaptation:** Mitra-Spacer-Transapical (Cardiosolutions) (Maisano *et al.* 2015), Middle Peak Medical, US

6.2 DEVICE DESCRIPTION

The HARPOON™ Beating Heart Mitral Valve Repair System, known hereafter as HARPOON System, is described in detail in the Instructions For Use (IFU). The IFU will be provided to the sites and Ethics Committees (ECs), and a copy is part of the Trial Master File and Investigator Site File.

6.2.1 REGULATORY STATUS

The HARPOON System is CE-marked. Its use in this study is consistent with the product's labelling.

6.2.2 INDICATION FOR USE

The HARPOON System is indicated to reduce the degree of mitral regurgitation in patients with severe MR caused by mid-segment posterior leaflet prolapse as a result of degenerative mitral valve disease by delivering and anchoring ePTFE chords to the prolapsed mitral valve leaflet in a beating heart.

6.2.3 TECHNICAL DESCRIPTION OF THE DEVICE

The HARPOON System consists of two parts: 1) HARPOON Introducer and 2) HARPOON Delivery System. Both items are essential for proper delivery of ePTFE implants in the mitral valve leaflet to eliminate or reduce mitral valve regurgitation (MR). The HARPOON System is a Class III product following rule 8 of the Annex IX of the MDD 93/42/EEC (intended to be used to deliver an implant in direct contact with the heart). For a detailed description of the HARPOON System, please refer to the HARPOON™ Beating Heart Mitral Valve Repair System Instructions for Use.

6.2.4 MANUFACTURE OF HARPOON INTRODUCER AND DELIVERY SYSTEM

The HARPOON System (Introducer and Delivery System) are manufactured by HARPOON Medical, an indirect wholly-owned subsidiary of Edwards Lifesciences Corporation.

6.2.5 HARPOON SYSTEM DEVICE DELIVERY AND USE

Please refer to the HARPOON™ Beating Heart Mitral Valve Repair System Instructions for Use for details of the system components and detailed procedure guidelines and instructions.

6.3 PRIOR CLINICAL EXPERIENCE WITH THE HARPOON SYSTEM: EFS AND CE MARK TRIALS

6.3.1 TRIAL INFORMATION

Two (2) ongoing European clinical trials have assessed the safety and performance of the HARPOON System: the Early Feasibility Study (EFS) and the CE Marking Trial (CE Mark, conducted under two (2) clinical protocols):

	Clinical Investigation Plan (CIP) Title	CIP Number(s)
EFS	Safety and Performance Study of the Harpoon Medical Transapical Suturing Device (TSD-5) in Subjects with Degenerative Mitral Regurgitation – Early Feasibility Study	HMFIM -1000-PL
CE Mark	Safety and Performance Study of the Harpoon Medical Transapical Suturing Device (TSD-5) in Subjects with Degenerative Mitral Regurgitation – CE Marking for the Harpoon Medical Device	HMFIM -1000-PL-02 and HMCE-1002-00

6.3.2 OBJECTIVES AND DESIGNS

The purpose of the EFS trial is to assess the safety and performance of the HARPOON System (previously the Harpoon Medical TSD-5 Device). The early data collected from the trial were used to power and support the design of the study to support CE Mark of the HARPOON System. The EFS is an open-label, prospective, non-randomized, multicenter European single-arm early feasibility study to demonstrate the performance and safety of the HARPOON System in subjects with degenerative mitral regurgitation. After implantation of the study device, subjects are followed at 30 days, 6 months, and annually for 3 years post-procedure.

The purpose of the CE Marking trial is to assess the safety and performance of the HARPOON System in subjects with severe degenerative mitral regurgitation by implanting ePTFE chords in the posterior leaflet of the mitral valve using a transcatheter approach via transapical access thereby obviating the need for open surgery and its risks. The CE Marking trial is an open-label, prospective, non-randomized, multicenter observational trial without concurrent or matched controls. Following a pre-surgical assessment, subjects are followed for 30 days to demonstrate that the study device performs as designed and has the ability to successfully implant one or more ePTFE chords on the mitral valve via a small left thoracotomy on the beating heart and reduce mitral regurgitation from severe to ≤ moderate at the conclusion of the procedure and at 30 days post-procedure. Subjects will be followed thereafter at 6 month intervals for a minimum of three (3) years post-surgical experience.

6.3.3 ENROLMENT AND FOLLOW-UP

This clinical experience summary is based on clinical data as of 02 April 2019 for subjects enrolled from 16 February 2015 (first enrolment in EFS) to 07 November 2017 (last enrolment in CE Mark).
Sixty-five (65) subjects were enrolled at six (6) investigational sites between both studies. This includes thirteen (13) subjects enrolled in the EFS study and fifty-two (52) subjects in the CE Mark study. Of the

enrolled population, sixty-two (62) subjects were implanted with the HARPOON System (thirteen (13) in the EFS trial and forty-nine (49) in the CE Mark Trial). Three subjects left the operating room without the investigational device. One case was aborted before the Harpoon procedure and 2 cases were converted to SOC mitral valve surgery.

Overall, follow-up compliance of 100% (56/56) of eligible subjects was achieved at the 1-year visit. Six (6) HARPOON System subjects were censored through 1-year including two (2) deaths and four (4) reoperations. Follow-up compliance of 98% (40/41) has been achieved so far at the 2-year visit; nine (9) subjects have yet to reach their 2-year follow-up window. Follow-up is currently ongoing.

6.3.4 SAFETY ENDPOINTS

Table 1 summarizes the early (≤30 POD) and late (>30 POD) complication rates for the trial safety endpoints for the implanted (HARPOON System) cohort. Early event rates are described as simple proportions; late event rates utilize linearized (person-year) rates.

Table 1: Prior Clinical Experience: Safety endpoints for the implanted cohort

Endpoint	Early (≤30 POD) N = 62 n,m (%/N)	Late (>30 POD) LPY = 99.0 n,m (%/pt-yr)
Mortality	1, 1 (1.6)	2, 2 (2.0)
Study Device Reoperation	1, 1 (1.6)	10, 10 (10.1)
Thromboembolism	0, 0 (0.0)	1, 1 (1.0)
Stroke	0, 0 (0.0)	0, 0 (0.0)
TIA	0, 0 (0.0)	0, 0 (0.0)
Non-cerebral Embolism	0, 0 (0.0)	0, 0 (0.0)
Endocarditis	1, 1 (1.6)	0, 0 (0.0)
Myocardial Infarction	3, 3 (4.8)	0, 0 (0.0)
Renal Failure	0, 0 (0.0)	0, 0 (0.0)

'n' is the number of subjects with the event;'m' is the number of events; LPY: late pt-yrs.
Early rates are reported as n/N; late linearized rates are reported as m/LPY

One (1) early (1.6%) and two (2) late (2.0%/pt-yr) deaths have been reported. The CEC has adjudicated one (1) early death with primary cause of death cardiac arrest, and not related to the study device. One of the two (2) late deaths was adjudicated as caused by aortic dissection and device related, and the second late death was a sudden death with unknown causality, and therefore was also counted as device related.

One (1) early (1.6%) and ten (10) late (10.1 %/pt-yr) reoperations have been reported, including nine (9) repairs and two (2) mitral valve replacements. See **Section 6.3.6.1** for more information on reoperations that have occurred. There were no reports of unanticipated adverse device effects.

6.3.5 PRIMARY PERFORMANCE RESULTS

In the EFS study, procedural success was defined as the subject leaving the operating room with at least one (1) ePTFE chord in place, having a Discharge MR grade of ≤ mild and 30 Day MR grade ≤ mild,

without a reoperation prior to 30 days. Procedural success was achieved in 84.6% (11/13) of the ENROLLED cohort.

In the CE Mark study, Procedural success was defined as the subject leaving the operating room with at least one (1) ePTFE chord in place, having a Discharge MR grade of ≤ Moderate and 30-Day MR grade ≤ Moderate, without a reoperation prior to 30 days. Procedural success was achieved in 88.5% (46/52) of the ENROLLED cohort.

6.3.6 SECONDARY PERFORMANCE RESULTS

6.3.6.1 MITRAL REGURGITATION

Table 2 presents the mitral regurgitation (MR) severities as evaluated by the Echo Core Lab at the baseline, discharge, 1-month, 6-month, 1-year, and 2-year follow-up visits for the HARPOON System cohort.

Several subjects with moderate to severe mitral regurgitation underwent re-operations and were identified as having ruptured ePTFE chords. An investigation was conducted to determine the root cause of ePTFE chord ruptures. The root cause of the chord ruptures was found to be over-tensioned chords. Findings confirmed that no material or device design changes were required. As a result of this investigation, screening and procedural updates to the IFU, Training Program Materials, and Post-Market Clinical Follow-up Study were made to mitigate future ePTFE chord ruptures.

Table 2: Prior Clinical Experience: Mitral Regurgitation Results

Visit	Severity	% (n/N)	Visit	Severity	% (n/N)
Baseline	None	0.0% (0 /57)	6 Month Follow-up	None	17.2% (10 /58)
	Trace	0.0% (0 /57)		Trace	34.5% (20 /58)
	Mild	0.0% (0 /57)		Mild	29.3% (17 /58)
	Moderate	7.0% (4 /57)		Moderate	10.3% (6 /58)
	Severe	93.0% (53 /57)		Severe	8.6% (5 /58)
Discharge	None	22.4% (13 /58)	1 Year Follow-up	None	9.6% (5 /52)
	Trace	51.7% (30 /58)		Trace	42.3% (22 /52)
	Mild	20.7% (12 /58)		Mild	23.1% (12 /52)
	Moderate	3.4% (2 /58)		Moderate	23.1% (12 /52)
	Severe	1.7% (1 /58)		Severe	1.9% (1 /52)
1 Month Follow-up	None	11.7% (7 /60)	2 Year Follow-up	None	2.6% (1 /38)
	Trace	50.0% (30 /60)		Trace	47.4% (18 /38)
	Mild	23.3% (14 /60)		Mild	15.8% (6 /38)
	Moderate	13.3% (8 /60)		Moderate	26.3% (10 /38)
	Severe	1.7% (1 /60)		Severe	7.9% (3 /38)

N represents the number of subjects with evaluable data at the specified visit.
If a subject has multiple assessments in the same visit window, the worst severity is summarized.

6.3.6.2 NYHA FUNCTIONAL CLASS

Performance was also assessed using NYHA functional classification change. At 1 year of follow-up, 92.3% of subjects were in NYHA class I, 5.8% were in NYHA class II, and 1.9% were in NYHA class III, corresponding to an improvement (50%) or maintenance (48%) of NYHA class for 98% (51/52) of subjects.

6.3.7 SUMMARY

The results of the EFS and CE Marking trials support the safety and performance of the HARPOON System.

7.0 STUDY DESIGN

7.1 OBJECTIVE

The objective of this study is to evaluate the long-term safety and performance of the HARPOON System for use in patients presenting with severe degenerative mitral regurgitation due to posterior leaflet prolapse in the post-market phase.

7.2 DESIGN

A single arm, prospective, multicentre, non-randomised and open-label, post-market study.

7.3 ENDPOINTS

The following are the planned endpoints for the study:

7.3.1 PRIMARY SAFETY ENDPOINT:

- Freedom from all-cause mortality, disabling stroke and life-threatening bleeding at 30 days post-implant.

7.3.2 PRIMARY PERFORMANCE ENDPOINT:

- Procedure success at 30 days post-treatment, as measured by: technical success with reduction of MR to less than or equal to mild and the absence of major device or procedure-related SAEs.

7.3.3 OTHER PLANNED ANALYSES:

- Technical success defined as survival and exit from the operating room (OR) with successful implantation of 3 or more expanded polytetrafluoroethylene (ePTFE) chords
- Freedom from major device or procedure-related serious adverse event (SAE) at 30 days, 1 year and 2 years post-implant
- Quality of Life (change from baseline to 1 and 6 months)
- 6-minute walk test (change from baseline to 1 and 6 months)
- Freedom from ePTFE chord rupture as reported by echo core lab at 1 year and 2 years post-implant
- Freedom from reoperation or re-intervention due to ePTFE chord rupture at 1 year and 2 years post-implant
- Functional improvement from baseline NYHA Functional Classification at 1 year and 2 years post-implant
- Freedom from reoperation or reintervention on the mitral valve annually through 5 years post-implant
- Freedom from ≥ moderate MR annually through 5 years post-implant

7.3.4 KEY ENDPOINT DEFINITIONS:

A complete list of definitions can be found in **Attachment A.** Key endpoint definitions include:

All-cause mortality:
Mortality for any cause will be reported with a further stratification by Cardiovascular and Non-Cardiovascular. All Deaths will be adjudicated for a cause of death and relationship to the investigational device and the index/implant procedure.

Cardiovascular mortality
Expirations for any of the contributing conditions such as Heart failure, Myocardial infarction, Major bleeding, Thromboembolism, Stroke, Arrhythmia and conduction system disturbance, Cardiovascular infection and sepsis (e.g., mediastinitis and endocarditis), Tamponade, Sudden, unexpected death Other cardiovascular, Device failure, Death of unknown cause (adjudicated as cardiovascular)

Noncardiovascular mortality
Any death in which the primary cause of death is clearly related to another condition such as Non-cardiovascular infection and sepsis (e.g., pneumonia,) Renal failure, Liver failure, Cancer, Trauma, Homicide, Suicide, Other non-cardiovascular causes.

Disabling Stroke
Stroke is defined as a focal or global neurological deficit lasting more than 24 h OR less than 24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological de*fi*cit results in death.

A disabling stroke includes any neurological deficit (for example partial visual field cut) with a modified Rankin scale score equal or more than 2 with an increase in equal 1 or more modified Rankin scale score category from individual's pre-stroke baseline at 90 days after stroke onset.

Life-threatening Bleeding
Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, intrathoracic, or pericardial necessitating surgery or intervention, or intra- muscular with compartment syndrome *OR* bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.

Fatal Bleeding: Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.

Major device or procedure related serious adverse event

All Major Serious Adverse Events adjudicated as device or procedure related, as defined by modified MVARC (Stone, et al.) including:

- Procedure or Device related Death
- Procedure or Device related Stroke
- Procedure or Device related Life-threatening bleeding (MVARC scale)
- Major vascular or access (index procedure) complications
- Major cardiac structural complications related or cause by device or procedure
- Procedure related Stage 2 or 3 acute kidney injury (includes new dialysis)
- Procedure related Myocardial infarction or coronary ischemia requiring PCI or CABG
- Procedure or device related severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure, treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for more than 48 h.
- Any device-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention including:
    - Structural or Functional failure of the HARPOON device, introducer or artificial chords (ePTFE) requiring an intervention.
    - Conversion to the Open Mitral Valve Surgery secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or Secondary to procedural complications (such as cardiac perforation, removal of an embolized artificial chords, injury to Aortic valve and so on)
    - Device malpositioning (Artificial chords malpositioning) requiring intervention. Permanent deployment of **artificial chord(s)** in a location other than intended or movement of the artificial chords during or post deployment which requires an intervention.
    - Artificial Chord detachment (used with HARPOON device) which requires an intervention
    - Device fracture: a break, tear, perforation, or other structural defect in the artificial chords (housing, leaflet, and so on) resulting in device failure, resulting in recurrent MR symptoms, or requiring reintervention.
    - Damage to the native mitral valve apparatus (damage to native chordae tendinae, Leaflets, Papillary muscles or Mitral annulus) requiring an intervention or conversion to Open Mitral Valve Surgery.
    - Symptomatic or requiring intervention Device Thrombosis (any thrombus attached or near the artificial HARPOON implanted chords)
    - Interaction with non-mitral valve intracardiac structures which requires intervention and
    - Endocarditis (as diagnosed by modified Duke endocarditis criteria or evidence of abscess, pus, or vegetation confirmed as secondary to infection

by histological or bacteriological studies during an operation or autopsy) which required a surgical intervention.
- Hemolysis (a presence of a leaflet perforation on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus increased haptoglobin and/or LDH levels; which lead to a surgical intervention.
- Other major device or procedure related SAEs

7.4 NUMBER OF SUBJECTS

Two-hundred and fifty (250) subjects will be implanted at up to twenty-five (25) centers in Europe. The enrolment period completion is anticipated to be two (2) years.

8.0 STUDY POPULATION

8.1 SUBJECT INCLUSION CRITERIA

A subject who meets ***all of the following criteria*** potentially ***may be included*** in the study:

1. Subject is ≥ 18 years old
2. Presence of severe MR as read on a transthoracic echocardiographic study
3. Mitral leaflet coaptation surface is sufficient to reduce mitral regurgitation without undue leaflet tension (approximate leaflet to gap ratio of 2:1) based on the judgment of the patient eligibility committee and the operating surgeon
4. Degenerative mitral valve disease with mid-segment P2 prolapse
5. Patient is able to sign informed consent and able to return for follow-up and is capable of participating in all testing associated with this clinical investigation

8.2 SUBJECT EXCLUSION CRITERIA

A subject who meets ***any of the following criteria will not be included*** in the study:

1. Patient is of the age where further growth is expected
2. Active endocarditis
3. Left ventricular or left atrial appendage thrombus
4. Severe mitral annular and/or leaflet calcification
5. Cannot tolerate procedural anticoagulation or post-procedure antiplatelet regimen
6. Mitral stenosis
7. Functional Mitral Valve disease
8. Previous mitral valve replacement surgery
9. Fragile or thinning apex
10. Contraindications to transesophageal echocardiography (atlantoaxial disease, severe generalized cervical arthritis, upper gastrointestinal bleeding, significant dysphagia and odynophagia, has received extensive radiation to the mediastinum).
11. Patient is pregnant or lactating

8.3 SCREENING AND ENROLMENT

All subjects who are clinically suitable for treatment with the HARPOON System, and who meet the study inclusion/exclusion criteria will be approached for inclusion in the study. (Subjects who do not wish to participate in the study may be treated with the HARPOON System outside of the study.) Subjects who agree to participate will sign an Ethics Committee (EC)-approved study informed consent and will be considered part of the enrolled population.

8.4 SUBJECT AND STUDY DURATION

The total enrolment period for this study is estimated to be two years, with an estimated start date in Q4 2019 and estimated completion in Q4 2021. Follow-up for implanted subjects is five years, therefore the entire study duration is seven years, with an estimated completion in Q1 2027.

9.0 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

9.1 SUBJECT SCREENING AND INFORMED CONSENT

All subjects who are clinically suitable for treatment with the HARPOON System and meet study eligibility requirements will be asked to participate in further screening and will sign a study-specific Ethics Committee (EC) approved study informed consent form.

A "Screening Log" is provided to the investigational sites to maintain a cumulative log of all screened subjects. For subjects who are ineligible for participation in the clinical investigation or choose not to participate, a reason supporting the disqualification of the subject shall be entered on the Screening Log. Sites are not required to enter any data into the EDC system for screen failures.

9.2 SCHEDULE OF ASSESSMENTS

The schedule of study assessments through the 60-month clinical follow-up is shown in **Table 3**. Details of selected assessments are provided below.

Table 3: Schedule of Assessments

Assessment	Baseline and Pre-operative	Surgery Date	7-Day or Discharge	30 Days (+ 20/-0 d)	6 Months (+/- 30 d)	12 Months (+/- 30 d)	18 Months (+/- 30 d)	24 Months (+/- 60 d)	36 Months (+/- 60 d)	48 Months (+/- 60 d)	60 Months (+/- 60 d)
Medical History	X										
3D Transoesophageal Echocardiogram (TOE)[1]	X	X									
Transthoracic Echocardiogram (TTE)	X		X	X	X	X	X	X	X	X	X
Patient Eligibility Assessment by Patient Eligibility Committee Report[2]	X										
NYHA Heart Failure Class	X			X	X	X	X	X	X	X	X
Physical exam	X		X	X	X	X	X	X	X	X	X
STS score risk assessment	X										
EURO score risk assessment	X										
Study Consent Signed	X										
Laboratory Assessments[3]	X										
Electrocardiogram (ECG)	X			X	X	X	X	X	X	X	X
6 Minute Walk Test	X			X	X						
SF-36 Quality of Life Assessment	X			X	X						
KCCQ Quality of Life Assessment	X			X	X						
Pregnancy test (if applicable)	X										
Medications & Dosage[4]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X

[1] The 3D TOE previously-completed as part of the standard of care to assess the patient's suitability for treatment with the HARPOON System will be collected as part of historical data in the study. This assessment does not need to be repeated for study purposes.

[2] As part of clinical assessment for suitability for treatment with the HARPOON System, the patient will have already undergone an assessment of TOE by a Patient Eligibility Committee (PEC) as part of the standard-of-care. The report from this assessment will be collected as part of historical data in the study.

[3] Laboratory assessments performed as part of the standard of care will be recorded including (if performed) WBC count, haemoglobin, haematocrit, platelet count, creatinine, INR, total albumin, total bilirubin, BNP, and NTproBNP.

[4] All cardiac medications will be recorded within the study. Changes in medications will be documented in the medication log within the EDC system.

9.3 SCREENING EVALUATIONS AND PATIENT ELIGIBILITY COMMITTEE

All screening testing and assessment to determine if a patient is suitable for treatment with the HARPOON System is conducted within the standard-of care at the hospital outside of the study. This assessment includes the review of the patient's 3D TOE by a Patient Eligibility Committee (PEC) who will independently assess the eligibility of the patient for general treatment with the device.

Only once a patient is confirmed to be eligible (Pass) for treatment with the HARPOON System, is the patient approached for inclusion in the post-market study. Once consented and enrolled, the results of the previously-conducted HARPOON System suitability screening will be recorded as historical data.

9.4 BASELINE/PRE-PROCEDURE EVALUATIONS

Once the subject has signed a study informed consent, data from the following assessments which would have already been conducted as part of the standard of care, will be recorded:

- Routine laboratory assessment (recording any of the following that are done as part of the standard of care: WBC count; haemoglobin haematocrit, platelet count, creatinine, INR, total albumin, total bilirubin, BNP, NTproBNP)
- Routine electrocardiogram (ECG)
- Routine physical examination
- Assessment of NYHA Heart Failure Class
- Transthoracic echocardiogram (TTE)
- 3D Transoesophageal echocardiogram (TOE)
- Patient Eligibility Committee report of the TOE
- Assessment of Medical History

The following baseline assessments will be conducted as part of the study following informed consent.

- Assessment of STS score risk
- Assessment of EURO score risk
- 6 Minute Walk Test
- Quality of Life Assessment - SF-36
- Quality of Life Assessment - KCCQ
- Assessment of cardiac medications
- Pregnancy test (if applicable)

9.5 TREATMENT/PROCEDURE ASSESSMENTS

9.5.1 PROCEDURE OVERVIEW:

The HARPOON System procedure will be conducted in accordance to the HARPOON System CE-Mark Instructions for Use.

The study investigator will be trained in device use through didactic, practicum training, and proctoring. Complete details on the preparation and use of the HARPOON System can be found in the device's Instructions for Use.

9.5.2 CONVERSION TO MITRAL VALVE SURGERY

If in the judgment of the operating surgeon, adequate MR reduction has not been achieved, or if for any other clinical reason, conversion to standard-of-care mitral valve surgery shall be performed. Subjects who undergo a conversion to standard-of-care mitral valve surgery shall continue safety assessments (all tests identified in this protocol at each follow-up visit) through 30 days or until resolution of any adverse events related to the procedure, and then exited from the study.

9.5.3 PRIMARY FOLLOW-UP ASSESSMENTS

Post-procedure management: Standard hospital protocols for the management of subjects after mitral valve surgery shall be followed.

7-Day/Discharge assessment: All subjects shall be discharged from the hospital at the discretion of the attending cardiac surgeon. Prior to discharge, all subjects shall undergo a comprehensive pre-discharge TTE as well as a physical exam on either day 7 or at the time of discharge, whichever occurs first.

Primary subject follow-up: Subjects shall be seen at 30 days (+20/-0 days) after the HARPOON System procedure. A TTE and specific clinical assessments, in accordance with the Schedule of Assessments, shall be performed at that time.

Additional clinical and TTE follow-up shall occur for all active subjects in accordance with the Schedule of Assessments at the following intervals:

- 6-months (+/- 30 days)
- 12-months (+/- 30 days)
- 18-months (+/- 30 days)
- 24-months (+/- 60 days)
- 36-months (+/- 60 days)
- 48-months (+/- 60 days)
- 60 months (+/- 60 days)

9.6 MISSED FOLLOW-UP

The Investigator(s) will make every attempt to follow the subjects. All subjects will be encouraged by the Investigator(s) to report any address or telephone number changes to the study site personnel. Subjects should be informed of the importance of returning for scheduled follow-up visits even if they are not having any medical issues.

If a subject cannot be reached for a follow-up visit, or misses a scheduled visit, and is not willing to go to a local hospital/clinic for protocol-required assessments, the visit will be recorded as a missed visit on the date of last attempted contact. The procedure for attempts at contact should be two phone calls made and recorded in the study medical record. Subjects who miss a visit will not be considered

withdrawn. Subjects who miss two (2) sequential follow-up visits may be considered lost to follow-up at the second missed visit, and exited from the study.

9.7 STUDY EXIT CRITERIA AND PROCEDURES

The reason for study exit will be documented on the appropriate case report forms and in the medical records for each subject who exits the study.

Subjects may exit the study for any of the following reasons:

- Screen Failure
- Device Attempted but Not Implanted
    - Enrolled subjects for whom the implant procedure was prematurely aborted (e.g., entered operating room and anesthesia induced, but study procedure not attempted) or the HARPOON procedure was attempted but device not implanted, will be followed for 30 days or until resolution of any adverse events related to the implant procedure, and then exited from the study.
- Device Reintervention or Explant
    - Subjects who have a surgical reintervention where the device is explanted will be followed for 30 days post-reintervention or until resolution of any adverse events related to the procedure, and then exited from the study.
- Completion per Protocol
- Withdrawal
    - Subject Withdrawal: The subject may voluntarily withdraw from the clinical study at any time, without penalty or loss of benefits to which they are otherwise entitled.
    - Physician Withdrawal: The Investigator also has the right to withdraw a subject if s/he feels it is in the best interest of the subject.
    - Sponsor Withdrawal: The Sponsor may prematurely terminate the study. Circumstances under which the Sponsor can suspend or stop this trial include, but are not limited to, low study enrolment or new information regarding safety or efficacy.
- Death
- Lost to Follow-up
    - If a subject cannot be reached for a follow-up visit, the Investigator will document the contact efforts made to the subject and/or effort to obtain hospital records in the appropriate electronic case report form.

For subjects who are lost-to-follow-up or withdraw early, Edwards may request the site to search

death registries as available or applicable per GDPR requirements and may request the site to obtain the death certificate, if applicable.

In all cases of withdrawal (as described above), withdrawn subjects will not undergo further study follow-up procedures after the time of study exit. A study subject who has been withdrawn from the study will not be replaced.

9.8 DEATH AND SURGICAL VALVE INTERVENTION

9.8.1 DEATH

In the event of subject death, every effort should be made to obtain a copy of a death summary/death certificate. Information on the cause of death will be determined by the investigator(s) and reported in the study EDC system.

9.8.2 SURGICAL VALVE INTERVENTION

In the event of explant/subject surgical valve intervention, every effort should be made to obtain a copy of the procedure notes as well as any accompanying imaging data (CT, echo). Information on the cause of explant/surgical intervention will be determined by the investigator(s) and reported in the study EDC system. Subjects who have a surgical reintervention or whose device is explanted will be followed for 30 days or until resolution of any adverse events related to the procedure, and then exited from the study. Effort should also be made to return any explanted study devices to the Sponsor for analysis by the Edwards Complaint Handling team. Return kits for explanted devices will be provided, upon request, by the Edwards Surgical Complaint Handling Department.

10.0 ENDPOINT ANALYSIS AND STATISTICAL METHODS

10.1 ANALYSIS POPULATION

The analysis population is the 250 subjects who were implanted and entered the HARPOON System procedure, regardless of procedure outcome. The analysis population excludes any subjects who signed the study consent (were enrolled) but were exited from the study prior to the procedure.

10.2 SAMPLE SIZE RATIONALE

Edwards has established a minimum sample size of 250 participants for this study. The rationale for this sample size can be viewed from two different perspectives: precision of estimation and statistical monitoring for product failure.

10.2.1 PRECISION OF ESTIMATION

Regarding precision of estimation, the relevant statistical properties for n=250 are straightforward. As with any descriptive study, the principal impact of sample size is on precision of estimation, typically expressed in terms of a confidence interval. Increasing sample size always improves precision; however, the corresponding gain in precision eventually is small when weighed against the increase in study cost, time and complexity. An ideal sample size represents a balance between resources, time and precision of estimation.

Simple rates and proportions, and their corresponding 95% confidence intervals are the most easily understood method of analysis for the primary outcomes (MR grade and major serious device- or procedure-related adverse events) as well as the various safety parameters, performance measures and subject outcomes measured in this study.

Observed rates from 2% (0.02) to 17% (0.17) represent the full range of event rates (or their compliments) likely to be observed in this study. Adopting a precision goal of 5% or better for the full range (2% to 17%) of rates that are likely to be observed, a sample size of 250 is reasonable. Regardless of the rate considered, there is a substantial improvement in precision as sample size is increased from 50 to 100. However, the amount of improvement is much smaller as the sample size is increased further.

10.2.2 STATISTICAL MONITORING FOR PRODUCT FAILURE

Chord failures, detected by echo, will be monitored in a semi-continuous manner to detect a suspicious failure rate as early as possible. Detailed echo screenings will be performed at discharge, 30 days, 6 months, 12 months, and beyond, including unscheduled echos as deemed appropriate due to clinical symptoms. An adaptive algorithm will be used to analyse the 12-month failure rate for the device. The sample size of 250 subjects provides greater than 80% power to detect an underlying failure rate of 10% or greater.

10.2.3 SAMPLE SIZE RATIONALE CONCLUSION

The sample size for this study (n=250) provides adequate support for statistical estimation of the safety parameters, performance measures and subject outcomes measured in this study

including the primary outcomes of MR grade and major serious device- or procedure-related adverse events. In addition, this sample size provides acceptable power for statistical monitoring of apparent product failure.

10.3 STUDY ENDPOINT TESTING

The following outlines the test outcomes for success/failure of each of the stated endpoints:

10.3.1 PRIMARY SAFETY ENDPOINT TEST:

Freedom from all-cause mortality, disabling stroke and life- threatening bleeding at 30 days post-implant.

10.3.2 PRIMARY PERFORMANCE ENDPOINT TEST:

Procedure success at 30 days post-treatment, as measured by: technical success with reduction of MR to less than or equal to mild and the absence of major device or procedure-related SAEs.

10.4 ADDITIONAL PLANNED ANALYSES

The following analyses are planned:

- Technical success defined as survival and exit from the operating room (OR) with successful implantation of 3 or more ePTFE chords
- Freedom from major device or procedure-related serious adverse event (SAE) at 30 days, 1 year and 2 years post-implant
- Quality of Life (change from baseline to 1 and 6 months)
- 6 minute walk test (change from baseline to 1 and 6 months)
- Freedom from ePTFE chord rupture as reported by echo core lab at 1 year and 2 years post-implant
- Freedom from reoperation or re-intervention due to ePTFE chord rupture at 1 year and 2 years post-implant
- Functional improvement from baseline NYHA Functional Classification at 1 year and 2 years post-implant
- Freedom from reoperation or reintervention on the mitral valve annually through 5 years post-implant
- Freedom from ≥ moderate MR annually through 5 years post-implant

To address the uncertainty around ePTFE chord rupture, an initial analysis of apparent product failure will be conducted once 50 patients achieve 12 months of follow-up. Thereafter, a failure analysis will be repeated for each subsequent 10 patients achieving 12 months of follow-up. The rates of apparent product failure will be deemed unacceptable if the lower limit of any 95% confidence interval at 12 months is above 6% (inclusive of 95% CI). It should be noted that “Failure” is defined conservatively as suspected ePTFE chord rupture based only on echo. Confirmation of a rupture, which requires reoperation, is not required.

10.5 STATISTICAL ANALYSIS METHODOLOGY

The primary safety and performance endpoints will be summarized by counts, percentages and corresponding 95% confidence intervals. Other categorical variables will be summarized by counts and percentages. Continuous variables will be summarized using means, medians, ranges and standard deviations. Time to event analysis, including survival probabilities and standard errors, will be estimated using the Kaplan Meier method. Time to event will be calculated in days and standard errors will use the greenwood algorithm.

Statistical calculations will be based on all available data. No missing value imputations are planned for the primary and secondary analyses will be performed. Missing month and days for adverse events will be imputed. Regarding the secondary endpoint, an initial analysis of apparent product failure will be conducted once 50 subjects achieve 12 months of follow-up. Thereafter, a failure analysis will be repeated for each subsequent 10 subjects achieving 12 months of follow-up. The rates of apparent product failure will be deemed unacceptable if the lower limit of any 95% confidence interval at 12 months is above 6%.

10.6 METHODS USED TO MINIMISE BIAS

The following methods are employed to minimise bias in the study:

10.6.1 INCLUSION BIAS

All patients clinically eligible for treatment with the HARPOON System device and who meet the study criteria will be offered inclusion in the study.

10.6.2 ENDPOINT EVALUATION

An independent Echo Core Lab will evaluate all echocardiograms performed as part of the protocol (and in particular in relationship to the Primary Performance Endpoint and the Secondary chord rupture monitoring endpoint), and an independent Clinical Events Committee will adjudicate all potential safety endpoints and reinterventions through 2-year follow-up.

10.6.3 REPORTED DATA VERACITY

Routine monitoring will be conducted for all reported data according to the study monitoring plan.

10.6.4 AVOIDING ANALYSIS BIAS

Statistical analysis will be conducted according to a pre-specified Statistical Analysis Plan (SAP).

10.6.5 PUBLICATION BIAS

The study will be registered at clinicaltrials.gov to ensure that publication of results will occur whether results are favourable or unfavourable to the sponsor.

11.0 SAFETY REPORTING

Subjects will be carefully monitored during the study for possible Adverse Events (AEs) from the time of the subject's enrolment to the completion of their participation in the study.

11.1 DEFINITIONS OF ADVERSE EVENTS AND DEVICE DEFICIENCIES

All adverse events will be fully investigated by the Investigator and classified in line with the definition of the ISO 14155:2011 below (**Table 4**).

Table 4: Adverse Event Definitions

Term	Definition
Adverse event (AE)	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.

Serious adverse event (SAE)	An adverse event that (ISO 14155):
	• led to a death,
	• led to serious deterioration in the health of the subject, that either resulted in
	  • a life-threatening illness or injury, or
	  • a permanent impairment of a body structure or a body function, or
	  • in-subject or prolonged hospitalization, or
	  • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
	• 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.

Device deficiency	Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
Device malfunction	Failure of an investigational medical device to perform in accordance

Term	Definition
	with its intended purpose when used in accordance with the instructions or use or CIP.
Adverse device effect (ADE)	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 device effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user NOTE 1: Use error includes slips, lapses, and mistakes. NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

11.2 CAUSALITY RELATIONSHIP

Relatedness of the AE to the index procedure or the HARPOON System device itself will be evaluated by the investigator.

The causal relationship of the AE to the device and the procedure will be rated as follows:

1) **Not related**: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;

- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) **Possible:** the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably have explained by another cause, but additional information may be obtained.

5) **Causal relationship:** the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

11.3 REPORTING ADVERSE EVENTS

11.3.1 REPORTING BY THE INVESTIGATOR

Adverse Event reporting to the sponsor is the Investigator's responsibility and will start at time of enrolment and will continue until a closure of the study follow-up or until a subject exits the study.

Adverse events will be recorded on the Electronic Case Report Form by the Clinical Study Coordinator (or any designated site personnel). If the system is not accessible, the event can be reported to sponsor by using the following e-mail address: ASCEND-Safety@edwards.com

AE information (start and stop date, description of event, severity, and relatedness to the HARPOON System procedure and the HARPOON System) will be assessed and **recorded** in the EDC system **in a timely manner** by the site. Whether an AE meets the definition for serious adverse event will be determined by the study investigator using the ISO 14155 definition (see **Table 4**). Relatedness of the AE to the index procedure or the HARPOON System device itself will be judged by the investigator by using the causality categories listed in Section 11.2.

The investigator shall notify the sponsor immediately and **not later than 3 calendar days** after the investigator has become aware of a SAE or device deficiency that might have led to a SAE by completing the Adverse Event electronic Case Report Form.

All reported events will be followed until resolution, stabilization or 30 days after the last subject implanted has completed the study, whichever occurs first.

11.3.2 SAFETY ASSESSMENT AND REPORTING BY THE SPONSOR

The Safety Overview and Process (Adverse Event Handling) in the ASCEND Study has been established as an independent two-level review of reported Adverse Events (AE) and Device Deficiencies conducted by the Sponsor's Safety Department and an independent clinical adjudication of potential safety endpoints (Death, stroke, bleeding) and reintervention post index procedure by the Clinical Events Committee (CEC). The process includes:

Adverse Event Review Upon receipt of Adverse Event (AE) notification (electronic EDC , email ASCEND-Safety@edwards.com), reported by the Investigator and/or Research Coordinator, Safety conducts a Sponsor Assessment of each AE on the AE Review form as per Regulatory requirements specific to the

study/region where the study is conducted, per MEDDEV 2.7/3 (Clinical Investigations: Serious Adverse Event Reporting), MEDDEV 2.12-1 rev 8 (Vigilance Reporting), ISO 14155-2011 (Clinical investigation of Medical Devices for Human Subjects) where applicable and internal EW standard operating procedures, including USADE decision and complaint reporting.

AEs are assessed as serious or non-serious, assessed for causality, and if anticipated or unanticipated. Any updated AE is re-assessed for seriousness, causality and if anticipated or unanticipated. In any urgent situation concerning patient's safety or to report an unanticipated adverse device effect (USADE), the sites can contact Edwards Surgical Safety, Safety Officer directly.

- **USADE Reporting** During Safety's AE review, any AE assessed as a USADE will be reported as soon as possible to EW Regulatory Affairs (RA) and by RA to the EU Regulatory Authorities within local regulatory requirements and timelines. Safety will notify all ethics committees and Investigators as required.

- **CRO Responsibilities** This study is monitored by an external CRO to ensure complete AEs and SAEs reporting through a monitoring process as identified/described in the monitoring plan, and to verify that all reported data are consistent and queries answered.

- **Complaint Reporting** In addition, as required in post market investigation, each AE will be assessed in regards to a device causality, and will be reported to the Edwards EU Complaint Handling group. EU Complaint Group will assess and report appropriately all device complaints to EU Authorities as per MEDDEV 2.12-1.

Clinical Events Committee (CEC) Adjudication During the Sponsor's Safety review potential safety endpoints and reinterventions are identified for adjudication. If an event meets the safety endpoint definition as specified in the protocol and CEC Charter (or can possibly be related to any safety endpoint, although reported as "Other"), the source documents are requested from the site to support CEC adjudication.

The CEC reviews forwarded events and their source documents to verify if additional records are required, and to determine if the event meets the safety endpoint definition (as in the CEC Charter). During this process non-reported events can be identified by the CEC and queried to Edwards Safety Team for additional information. CEC activities are outlined in the CEC Charter.

11.3.3 SAFETY REPORTING TO AUTHORITIES

Depending on the local requirements or following agreement between both parties, the sponsor or the principal investigator will be responsible for performing safety reporting to the Ethics Committees according to the relevant local regulatory requirements.

The sponsor or sponsor designee will report all reportable Events to the National Competent Authority in accordance with the Medical Device Directive and all applicable official guidelines and national regulations.

11.4 CLINICAL EVENTS COMMITTEE ADJUDICATION

The study will have an independent Clinical Events Committee (CEC) whose role it will be to review all potential safety endpoints and reinterventions through 24-month follow-up for final safety endpoint evaluation as well as device and procedure relatedness. All CEC activities and the detailed adjudication process is regulated by the CEC Charter.

12.0 DEVICE DISTRIBUTION, ACCOUNTABILITY, AND REPORTING

12.1 DEVICE TRACEABILITY

Each component of the HARPOON System will be traceable via a lot number. Lot numbers are assigned according to date of manufacture and/or sterilization.

Records of device shipments will be maintained at Edwards Lifesciences in accordance with Quality System and internal procedures. As the HARPOON System to be used in this study has CE mark, device accountability records will not be required as the device is non-investigational. Lot numbers of devices used in/implanted in study subjects will be recorded within the study to provide traceability.

12.2 DEVICE MALFUNCTIONS AND FAILURE – VIGILANCE REPORTING

Should any device defect or malfunction be noticed at any point, whether prior to, during, or after a procedure, this defect or malfunction will be reported through the Edwards Lifesciences standard vigilance reporting process.

13.0 BENEFITS AND RISKS

13.1 BENEFITS

13.1.1 BENEFITS OF THE HARPOON SYSTEM AS COMPARED TO ALTERNATIVE TREATMENTS

Mitral valve regurgitation (MR) results in volume overload on the left ventricle, which in turn leads to ventricular dilation, decreased ejection performance, pulmonary hypertension, symptomatic congestive heart failure, atrial fibrillation, right ventricular dysfunction and death. Successful mitral valve repair restores mitral valve competence, eliminates volume overload on the left ventricle, improves symptom status and prevents adverse left ventricular remodelling. MR is corrected either by surgical open repair or replacement with a surgical mitral valve. Conventional mitral valve repair is performed with the support of cardio-pulmonary bypass (CPB). The key clinical benefit of the HARPOON System is the elimination of need for CPB to perform mitral valve repair for reduction of MR which in turn provides relief from the symptoms of severe degenerative mitral valve disease. HARPOON System facilitates mitral valve repair on a beating heart through a small incision without the need for CPB, thereby potentially reducing the perioperative complications such as wound infection, sternal dehiscence, bleeding, blood transfusions, cerebrovascular events, and renal failure.

Compared with surgical valve replacement, mitral valve repair has the following advantages:

- Lower operative mortality
- Improved left ventricular function
- Lower risk of stroke
- Lower risk of infection
- Freedom from anticoagulation and reoperation
- Superior long-term survival

While surgical mitral valve repair remains the gold standard, transcatheter techniques have the potential to decrease invasiveness and surgical morbidity, with shorter procedure and recovery times, while maintaining comparable performance.

The HARPOON System facilitates echo image-guided placement and anchoring of ePTFE chords on the mitral valve leaflets, offers a simplified technique for off-pump repair of degenerative MR, image-guided placement and anchoring of the chords, and real-time beating heart titration of the artificial chordae length to maximise leaflet coaptation and minimise mitral regurgitation. The technology provides:

- a low profile 9 Fr delivery system;
- secure anchoring of the artificial chordae to the mitral leaflet with a proprietary “bulky knot” anchor;
- easy to use delivery system that can implant an artificial ePTFE chord anywhere on the leaflet without the need to “catch” a moving leaflet;
- ability to implant multiple artificial chords via a haemostatic valve to minimise blood loss; and

- real-time, image guided adjustment of artificial chord length to maximise leaflet coaptation and minimise residual MR.

The HARPOON System provides a treatment method for degenerative mitral valve disease without the need for a sternotomy, cardio-pulmonary bypass, aortic cross-clamping and cardiac arrest.

It is therefore expected that the risks and the long-term discomfort associated with open heart surgery will be reduced because the HARPOON System is implanted using a less invasive procedure compared to classical open-heart surgery. These innovations result in a simpler procedure and may reduce trauma to the heart and blood loss.

13.1.2 BENEFITS OF PARTICIPATING IN THE ASCEND STUDY

As this study is a post-market study, the patient will receive treatment with the HARPOON System whether or not s/he takes part in this study. As part of the study, subjects would receive a higher level of echo imaging and clinical follow-up than they would outside of the study environment. They also have a dedicated clinical research team following their progress. Finally, an additional benefit in participating in the study is that it furthers knowledge of this treatment. The study may also allow the subject to receive therapy with this device and procedure with potentially lower complications than conventional method which in turn may benefit other patients in the future.

13.2 RISKS

13.2.1 HARPOON SYSTEM PROCEDURE RISKS

Prior evaluation in early feasibility and CE mark studies demonstrated reduced blood loss, reduced blood transfusions and no episodes of acute renal failure on comparison with conventional approaches to mitral valve repair. However, the HARPOON System implantation procedure may result in failures such as recurrence of MR or complications similar to commercially available devices with similar indications for use. Like any other new device, failures are related to factors such as learning curve, technical problems, procedural changes, and limited expertise with an investigational device. Risks are related to recurrence of MR secondary to rupture of ePTFE chords as previously described. Root cause analysis of chordal ruptures led to implementation of specific changes to case selection, pre-procedural screening, selection of appropriate echo-imaging technology to support the procedure, and procedural steps.

Physicians routinely discuss the risks associated with the use of general anaesthetic and the procedure itself during the process of acquiring informed consent from a patient. Anticipated adverse events are discussed in section 13.2.2.

13.2.2 ANTICIPATED ADVERSE DEVICE EFFECTS

The Potential Adverse Events that may be associated with the use of the HARPOON System include but are not limited to the following conditions and their symptoms:

- Abnormal lab values
- Allergic reaction/Hypersensitivity to contrast media, medication or device materials
- Anaemia

- Angina
- Arrhythmia or Conduction Disorders
- Artificial Chord(s) (ePTFE) Detachment
- Artificial Chord(s) embolization, migration, malposition or deployment in unintended location
- Artificial Chord(s) (ePTFE) Rupture or Breakage
- Bleeding
- Cardiac Arrest/Cardiogenic Shock
- Conversion to standard valve repair surgery or valve replacement
- Damage to cardiovascular tissue/Cardiovascular injury
- Damage to native chords (chordae tendinea)
- Damage to native mitral valve apparatus
- Device (artificial chord(s)) migration - etopic
- Device (artificial chords) thrombosis
- Dyspnoea
- Embolization (air, calcific, material, thrombus, etc.)
- Endocarditis
- Exercise intolerance or weakness
- Failure to deliver ePTFE artificial chord to the intended leaflet site
- Fever
- Heart Failure
- Hematoma
- Hemodynamic compromise
- Haemolysis
- Haemothorax
- Hypertension
- Hypotension
- Infection
- Inflammation
- Injury to Left Atrium
- Injury to Left Ventricle
- Injury, perforation or damage of mitral valve or leaflets
- Interaction with non-mitral valve intracardiac structures
- Left Ventricular outflow tract obstruction
- Mitral Regurgitation
- Mitral Stenosis
- Multiorgan failure
- Myocardial Infarction
- Nerve injury
- Oedema
- Other device functional malfunction with recurrent MR more than mild
- Other structural deterioration of the device with recurrent MR more than mild
- Pain at the incision site
- Pericardial damage

- Pericardial tamponade
- Pericarditis
- Pleural Effusion
- Pulmonary embolism
- Reaction to anaesthesia
- Recurrent Mitral Regurgitation
- Renal failure/insufficiency
- Reoperation or emergency cardiac surgery
- Respiratory event
- Stroke/TIA
- Sudden Death
- Syncope
- Thrombosis
- Transvalvular flow disturbance

Anticipated conditions may require medical treatment, intervention including surgery, or resolve in death or serious deterioration in the health of the subject.

13.2.3 RESIDUAL DEVICE AND PROCEDURE RISKS

On the basis of the risk analysis following the implementation of risk control measures, Edwards Lifesciences has identified a number of residual risks. Most of these are typical of the potentially severe consequences associated with any cardiac procedure, but the likelihood of occurrence was considered to be remote. These included damage to cardiac tissues or the introduction of air into the circulation, due to procedural error. Similarly, the possibility of sterility being compromised is a remote risk with any surgical device.

13.2.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE STUDY

Participation in the ASCEND study carries additional assessments and imaging above the standard-of-care. Specifically, study subjects will be assessed via transthoracic echocardiogram (TTE) more often than they would outside of a clinical study. The risk of TTE, however, as it is based on ultrasound technology, is minimal. Other than the TTE, all other study-specific assessments are simply clinic and physical assessments that would be within the range of standard follow-up of patients with a MR history.

An additional risk of participating in a clinical study is the risk of a lapse of confidentiality or exposure of personal identifying information. Mitigation of this risk is noted in section 13.3.

13.3 MINIMISING SUBJECT RISK

Several safeguards are incorporated into the study to minimize subject risk.

The HARPOON System has been studied in two pre-market studies and the device is being used in this study within the CE-marked indication for use.

Prior to subject screening and within the standard of care, patients are assessed for clinical suitability for treatment with the HARPOON System by an independent Patient Eligibility Committee (PEC) to minimise the risk of known adverse device effects. Only once eligibility for treatment has been confirmed are patients approached for inclusion in this post-market study. Within the study, routine echocardiographic monitoring of subjects also mitigates the risk of adverse device effects. An independent Clinical Events Committee will review all potential safety endpoint events and reinterventions, which allows a higher degree of monitoring of such risks throughout the study.

Subject risk specific to the functioning of the device has been mitigated through a documented didactic and hands-on training programme for surgeons on the device and surgical technique, in alignment with the IFU as provided by Edwards Lifesciences. In addition to other device use specifics, the training includes the requirement of the implantation of 3 chords, the use of trans-oesophageal echocardiography (TOE) prior to and during the procedure, and direction on the appropriate tensioning of the chords to minimise the risk of device malfunction.

The risk of lapse of patient confidentiality is mitigated by use of anonymised patient identification numbers (IDs) so that no personal-identifying information is entered into the electronic data capture (EDC) system, which is only accessible by trained study personnel. Study records including personal identifying information will only be accessible to the site study team and monitors during routine monitoring of the data. The transmission of study imaging utilises a software that ensures that images are appropriately anonymised prior to transmission. Any publication of the study data will include aggregate results only and will not include any identifying information.

13.4 JUSTIFICATION OF CLINICAL STUDY

The risk involved in the clinical study is minimised due to the fact the device being used is CE-marked and the study design falls within the intended use population. Subjects can still receive the same device treatment outside of the study. The risk of participating in the study is only minimally increased as compared to receiving the device outside the study, as there is a higher degree of imaging (TTE) and clinical assessment than would be present otherwise. Additionally, there are the risks involved in data collection. These risks, though, have been mitigated by the benefit of additional clinical follow-up and closer care, as well as procedures which have been put in place to protect subjects' personal information.

14.0 STUDY AND DATA MANAGEMENT

14.1 ECHOCARDIOGRAPHY CORE LAB

The Echocardiography Core Lab is responsible for independently evaluating all baseline, procedural and follow-up echocardiograms submitted by study sites. The purpose of the Core Lab is to ensure unbiased, timely and consistent analysis of the diagnostic data, and for evaluating changes in subject status over the course of the study.

Echocardiograms will be sent directly from the investigational sites to the Core Lab via an image transfer software. The Core Lab will enter the data into the electronic case report form (eCRF).

14.2 CLINICAL EVENTS COMMITTEE

The ASCEND Clinical Events Committee (CEC) is an independent institutionalized adjudicator who conducts real-time ongoing review of all potential safety endpoints and reinterventions. The review is done by independent reviewers, physicians ranging in speciality from interventional cardiology, structural heart radiology, and cardiac surgery. The activities of the CEC along with the definitions and detailed process are described in the CEC Charter.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol. The Investigator is not allowed to deviate from the study protocol except as specified in 5.6.4 c ISO 14155, to protect the rights, safety and well-being of human subjects under emergency circumstances.

Deviations shall be reported to the study Sponsor regardless of whether medically justifiable or taken to protect the subject in an emergency. Investigators will adhere to procedures for reporting study deviations to the EC in accordance with their specific reporting policies and procedures.

For reporting purposes, deviations are classified as major or minor:

14.3.1 MAJOR DEVIATIONS

A major protocol deviation (PD) or noncompliance is one that may have a significant impact on subject safety, well-being, the subjects' willingness to participate in the study, or that may compromise the integrity of the study data and analysis. Examples include:

- Subject implanted/treated with study device not having met eligibility criteria at the time of implant/treatment.
- Informed Consent not signed or signed after the initiation of non-standard of care, research related assessments.
- USADE not reported to EC/Sponsor within the required timeframe
- Unauthorized use/implant of an investigational device

14.3.2 MINOR DEVIATIONS

A minor protocol deviation or noncompliance is unlikely to have a significant impact on subject safety, well-being, or is unlikely to compromise the integrity of the study data and analysis.

14.4 STUDY CONDUCT, TRAINING, MONITORING RESPONSIBILITIES AND CONFIDENTIALITY

The study will be conducted in accordance with the applicable regulations and guidelines as set forth in Section 15 and this protocol. The study investigators are responsible for obtaining the appropriate regulatory approvals (ethics committee and where applicable to Competent Authority) prior to initiation of the study. The Investigator provides current copies of the study protocol to all sub-Investigators or other staff responsible for study conduct.

14.4.1 SITE INITIATION AND TRAINING

Site staff will be trained and experienced to perform their delegated tasks. Training may be in person, webinar, read and review, or other methods as deemed appropriate.

Training is documented on an "Individual Training Log." An "Individual Delegation of Authority Form" is completed at each site for each study staff individual designating which specific clinical study related tasks may be performed. The delegated tasks will determine what the training requirements are for each member of the study support staff. Technicians performing the echocardiograms do not require any additional training to perform the study tests, as the requested procedures are standard clinical exams used in standard practice.

New research staff members may be trained by previously trained personnel on the study protocol and procedures.

Site Initiation will not be complete until the surgeons who will be operating the HARPOON System device are confirmed as trained. The training may occur outside of the study training, but documentation of that training must be present in the study regulatory binder file prior to site initiation being completed.

14.4.2 MONITORING

Edwards Lifesciences personnel (or designee) will conduct site monitoring in accordance with the ASCEND Monitoring Plan to ensure that all investigators are in compliance with the protocol. Monitoring visits to the study site will be made periodically during the study. The monitor will ensure that the study sites adhere to ISO 14155 and all aspects of the protocol, including the accurate recording of results, the reporting of adverse events and device traceability.

The investigator agrees that representatives of the sponsor and appropriate regulatory agencies will be given direct access to source documents. The study site may also be subject to an audit by or on order of the sponsor as well as inspection by regulatory agencies. It is important that the investigators and their study personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

14.4.3 SUBJECT AUTHORIZATION AND CONFIDENTIALITY

Subject authorization and written informed consent must be obtained prior to the subject's enrolment into the study and in accordance with GCP, ISO 14155, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies. Subject confidentiality must be maintained in accordance with ISO 14155, GCP, GDPR, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.

14.4.4 INVESTIGATOR CONFIDENTIALITY

Study investigators must comply with the applicable provisions of the study agreement with regard to non-disclosure and confidentiality.

14.5 DOCUMENTATION REQUIREMENTS

14.5.1 SOURCE DOCUMENTS

Clinical regulations require that Investigators maintain information in the clinical study subject's medical records that corroborate data collected on the eCRF. Some examples of critical information to be maintained for possible review by regulatory inspectors are:

- Medical history and physical condition of the clinical study subject before involvement in the clinical study, sufficient to verify protocol entry criteria
- Dated and signed notes in the subject's medical record on the day of entry into the clinical study
- Dated and signed notes, test reports, procedure and intervention reports, from each clinical subject visit with reference to the eCRF for further information, if appropriate (for specific results of procedures and exams)
- Notes regarding concomitant anticoagulant/antithrombotic medications taken during the clinical study
- Subject's condition upon completion of or withdrawal from the clinical study
- Visit report and admission and discharge summaries for any reported SAE or potential endpoint
- All relevant documentation from Index admission including Harpoon index/implant procedure. Any additional intervention/procedure reports, if applicable, and index/implant discharge summary.

To protect subject confidentiality, the subject's name must not appear anywhere on the imaging media sent to study Sponsor e.g. prepared for evaluation by the core lab. All other subject identifiers (i.e. medical record number, personal number) are to be obscured. Original copies of all data must be kept at the site.

14.5.2 STUDY DOCUMENTS

The study Sponsor will provide pre-printed or electronic forms to each study site for documentation of:

- Investigator and site training to the protocol (Individual/Group Training Log)
- Authorized study site personnel (Individual/Group Delegation of Authority)

- Subject consent and screening (Screening and Enrolment Log)
- Visit tracking (Site Visit Log)

The site visit is recorded on the appropriate site visit log, a copy of which is sent to the Sponsor. During the course of the study, all correspondence regarding the study must be maintained in the regulatory binder provided by the study Sponsor. Emails may be archived electronically on CD/DVD. This regulatory binder must be made available for possible audits.

14.6 DATA COLLECTION

All required data for this study are to be collected with standardized Case Report Forms (CRF) for individual subjects**.** Electronic CRF (eCRF) will be utilised for this study. If for any reason an eCRF is unavailable and/or inaccessible, a paper CRF will be provided by the study Sponsor to be completed, signed by the Principal Investigator or designee, and submitted to the Sponsor.

The Edwards Lifesciences data management group is responsible for database development, edit check programming, validation, database maintenance, and statistical support. The application provides the capability of data collection remotely through the Internet so the participating site personnel may log on to the system securely with digital signature and audit trail, enter data, and answer/resolve data discrepancies/queries online. Other programming and/or data analyses will be done in the database system through the study Sponsor's internal network.

14.7 DATA AND DOCUMENT RETENTION

Study-related correspondence, subject records, consent forms, and source documents are to be maintained on file by the study site. The study Sponsor requires that it be notified in writing if the Principal Investigator wishes to relinquish ownership of the data and information so that mutually agreed upon arrangements can be made for transfer of ownership to a qualified entity. Records of each subject's participation in the study must be maintained for no less than a period of two (2) years after study closure and submission of the final report to the EC, or longer, as dictated by local regulations.

14.8 STUDY PROTOCOL AMENDMENTS

Changes in the protocol affecting the study outcome are made only by written amendment agreed upon by the study Sponsor, the applicable regulatory agency, and if pertinent, the EC. As appropriate, the study Sponsor will submit changes in the protocol and investigators will obtain EC re-approval. A report of withdrawal of EC approval must be submitted to the study Sponsor **within five (5) business days.** Any major revisions to the protocol, must be approved by the Sponsor and the EC.

14.9 STUDY COMPLETION

A final clinical report shall be compiled once data collection is complete. Such reports include all information required and outlined in this protocol. The final report will be provided to the ethics committees and other regulatory agencies as per applicable laws. The final clinical report will be filed in the clinical study master file.

14.10 FUTURE PLANS

No changes are planned at this time.

15.0 STATEMENTS OF COMPLIANCE, CONFIDENTIALITY AND RESPONSIBILITIES

15.1 APPLICABLE REGULATIONS AND GUIDELINES

This study will be conducted in compliance with the regulations set forth in **Table 5** and with country specific laws; whichever will afford greater protection to patients screened for participation in the clinical study and patients who participate in the study.

Table 5: Regulations and Guidelines

Country Region	Regulation / Guideline
Europe	- Directive 93/42/EEC on Medical Devices (MDD) - General Data Protection Regulation (EU) 2016/679 (GDPR) - MEDDEV 2.12-1 rev 8 Guidelines on a Medical Device Vigilance System - MEDDEV 2.12/2 Post Market Clinical Follow-up studies: A Guide for Manufacturers and Notified bodies - MEDDEV 2.7.1 Clinical Evaluation: A Guide for Manufacturers and Notified bodies - Declaration of Helsinki (2013) - EN ISO 14155:2011 Clinical Investigation of medical devices for human subjects Part 1: General requirements* - All applicable local and national laws and requirements in the participating countries - MEDDEV 2.7/3 Clinical Investigations: Serious Adverse Event Reporting, as applicable - MEDDEV 2.7/4 Guidelines on Clinical Investigation

*Exception to ISO 14155: all devices used in this study are CE marked therefore device accountability records will not be maintained.

Principles protecting the rights, safety and well-being of human patients, shall prevail over interests of science and society, and shall be understood, observed, and applied at every step in the clinical study.

The study shall not begin until the required approval/favourable opinion from the EC and applicable regulatory authorities have been obtained, where appropriate. Any additional requirements imposed by the EC or regulatory authorities shall be followed.

15.2 DATA PROTECTION AND PATIENT CONFIDENTIALITY

The Sponsor is dedicated to maintaining the confidentiality and privacy of patients who volunteer to participate in the study. The Investigator is responsible for maintaining confidentiality throughout the clinical study.

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient (patient identifiers include, but are not limited to: patient's name/initials, social security number or equivalent, and medical/hospital number). Authorized personnel assigned by the Sponsor will have

access to the confidential files and will have the right to inspect and copy all records pertinent to this study.

With respect to data protection and patient confidentiality, Sponsor, Institution and all Study Personnel will comply with applicable requirements (for example, the General Data Protection Regulation 2016/679 ("GDPR") for EU patients), including providing notice and obtaining patient consent regarding the processing of their personal data.

15.3 INVESTIGATOR RESPONSIBILITIES

The study Investigator(s) shall ensure that all work and services herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The Investigator will adhere to the study protocol, ISO 14155, GDPR, and compliance with applicable government and institutional regulations. The study Investigator(s) is responsible for obtaining appropriate regulatory approvals and reporting to regulatory authorities per all applicable regulations.

The Investigator is responsible for ensuring that this clinical study is conducted according to the Clinical Trial Agreement, Protocol, all conditions of regulatory and EC/IRB approval and applicable regulations. Written EC approval of the protocol and consent forms must be provided to the Sponsor prior to the enrolment of any subject in the clinical study at each site. The Investigator is responsible for ensuring that informed consent is obtained from all subjects prior to any diagnostic tests or treatments that are outside the standard course of treatment that would be followed if this subject was not being considered for enrolment in this clinical study. Periodic reports should be provided to reviewing boards and deviations reported per institution's EC policy.

Subjects must be informed that their medical records will be subject to review by the Sponsor, its authorized designee or regulatory agencies. Subjects will be informed that they are free to refuse participation in this clinical study without loss of benefits to which they are otherwise entitled, and that if they choose to participate, they may withdraw at any time without prejudice to future care. The informed consent will be provided by each site's EC and consent must be obtained by the subject. The original signed informed consent for each subject must be retained by the Investigator and is subject to review by the Sponsor. A copy of the informed consent will be provided to the subject.

The Principal Investigator (or designee)/Institution should maintain the study documents as specified in ISO 14155 or as required by applicable regulatory requirement(s). The Principal Investigator (or designee)/Institution should take measures to prevent accidental or premature destruction of these documents.

15.4 SPONSOR RESPONSIBILITIES

The study Sponsor will adhere to the study protocol, ISO 14155, GDPR, and compliance with applicable government and institutional regulations. The study Sponsor is responsible for obtaining appropriate regulatory approvals and reporting to regulatory authorities per all applicable regulations. The Sponsor is responsible for ensuring that this study will be conducted in compliance with all applicable local and

European regulations including but not limited to those listed in **Table 5.** The Sponsor will submit progress and final reports to EC's and Regulatory Authorities as required, if applicable.

The Sponsor will provide Investigators with the information and training required to conduct the clinical study properly and in accordance with the Clinical Investigational Plan (protocol) and any amendments, if applicable. The Sponsor must ensure that EC approval is obtained and remains current, and that the reviewing boards are informed of significant new information about the clinical study.

The Sponsor clinical study manager is responsible for the conduct and administration of this clinical study. These responsibilities include maintaining regular contact with each study site to ensure compliance with this Clinical Investigational Plan and verify that data are reported in a timely manner.

This study does collect safety/adverse event information which will be reviewed by the Sponsor's Safety Department along with relevant source documents provided by the sites. However, in addition to protocol-specified reporting, any complaint associated with an Edwards product will be forwarded to the Edwards Lifesciences complaint handling group. The complaint handling procedure should be followed.

16.0 PUBLICATIONS

HARPOON Medical, an indirect wholly-owned subsidiary of Edwards Lifesciences Corporation, as the study Sponsor on record, has a proprietary interest in this study. Authorship and manuscript composition will reflect cooperation between multiple investigators and sites, core laboratories, and Edwards Lifesciences. Authorship will be established prior to the writing of the manuscript.

All information related to the study is considered confidential and remains the sole property of Edwards. This includes but is not limited to the patent applications and the manufacturing process of HARPOON System. The investigator agrees to use this information only for purposes of this study. Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards. If Edwards approves the publication or presentation of the overall clinical study results and/or study specific results, then Institutions and Investigators will comply with the Publication and Public Disclosure Section of the Clinical Trial Agreement. Edwards may provide statistical support for the publication process.

17.0 REFERENCES

AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali Italy. 2015. Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation. European Network for Health Technology Assessment.

Andalib, A, S Mamane, I Schiller, A Zakem, D Mylotte, et al. 2014. A systematic review and metaanalysis of surgical outcomes following mitral valve surgery in octogenarians: implications for transcatheter mitral valve interventions., *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*, 9: 1225-34.

Gammie, J. S., P. Wilson, K. Bartus, A. Gackowski, J. Hung, et al. 2016. Transapical Beating-Heart Mitral Valve Repair With an Expanded Polytetrafluoroethylene Cordal Implantation Device: Initial Clinical Experience, *Circulation*, 134: 189-97.

Lam, Y-Y, P-W Lee, G Yong, and B P Yan. 2011. Investigational devices for mitral regurgitation: state of the art., *Expert Review of Medical Devices*, 8: 105-14.

Maisano, F, O Franzen, S Baldus, U Schafer, J Hausleiter, et al. 2013. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe., *Journal of the American College of Cardiology*, 62: 1052-61.

Nishimura, R. A., A. Vahanian, M. F. Eleid, and M. J. Mack. 2016. Mitral valve disease--current management and future challenges, *Lancet*, 387: 1324-34.

Nishimura, Rick A., Catherine M. Otto, Robert O. Bonow, Blase A. Carabello, I. I. I. John P. Erwin, et al. 2014. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart DiseaseA Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *Journal of the American College of Cardiology*, 63: e57-e185.

Stone, Gregg W. M.D., Adams David H. M.D., et al. 2015. Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2; Endpoint Definitions A Consensus Document from the Mitral Valve Academic Research Consortium. Journal of American College of Cardiology Vol 66, NO, 3. ISSN 0735-1097.

Vahanian, Alec, Ottavio Alfieri, Felicita Andreotti, Manuel J. Antunes, Gonzalo Baron-Esquivias, et al. 2012. Guidelines on the management of valvular heart disease (version 2012), *The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)*, 33: 2451-96.

Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30(4):303-371.

ATTACHMENT A – DEFINITIONS

ACCESS SITE AND VASCULAR COMPLICATIONS

I. Vascular complications

A. Major access site vascular complications, including:

- Aortic dissection or aortic rupture, or
- Access site-related arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment, or
- Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or
- Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment

B. Minor access site vascular complications, including:

- Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischemia; or neurological impairment, or
- Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or
- Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

II. Cardiac structural complications due to access-related issues

A. Major cardiac structural complications, including cardiac perforation (including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle) or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention

B. Minor cardiac structural complications, including cardiac perforation (including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle) or pseudoaneurysm not meeting major criteria

ACUTE KIDNEY INJURY

Maximal change in sCr from baseline to 7 days post-procedure:

- Stage 1: Increase in sCr to 150%–199% (1.50–1.99 x increase vs. baseline), increase of ≥0.3 mg/dl (≥26.4 mmol/l) within 48 h, or urine output <0.5 ml/kg/h for ≥6 h but <12 h

- Stage 2: Increase in sCr to 200%–299% (2.00–2.99 x increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but <24 h
- Stage 3: Increase in sCr to ≥300% (>3.0 x increase vs. baseline), sCr of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

ARRHYTHMIAS AND CONDUCTION SYSTEM DISTURBANCES

For emerging mitral valve procedures in which the frequency of major arrhythmias and conduction system disturbances is unknown, continuous rhythm monitoring for at least 48 h in the post-procedural period is recommended to maximize the detection of arrhythmias and conduction system disturbances. Data elements to be collected for all patients should include:

- Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), ventricular arrhythmias, and the presence of permanent pacemaker and implantable defibrillators. The type of permanent pacemaker should be recorded (e.g., single vs. dual chamber, biventricular).
- Procedure-related new or worsened cardiac conduction disturbance (including first-, second- [Mobitz I or Mobitz II], or third-degree AV block; incomplete and complete right bundle branch block; intraventricular conduction delay; left bundle branch block; left anterior fascicular block; or left posterior fascicular block, including heart block) requiring a permanent pacemaker implant; each subclassified as persistent or transient
- New-onset atrial fibrillation (or flutter) which lasts sufficiently long to be recorded on a 12-lead electrocardiogram, or at least 30 s on a rhythm strip.
- New-onset ventricular tachycardia or fibrillation
- Pacemaker or defibrillator lead dislodgement

Arrhythmias and conduction system disturbances are subclassified according to:

- The occurrence of hemodynamic instability
- Need for therapy including electrical/pharmacological cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate control therapy)
- Need for new permanent pacemaker and/or defibrillator implantation, including the indication(s) and the number of days post-implant. For patients with defibrillators, the number of appropriate and inappropriate shocks should be recorded.

ATRIAL FIBRILLATION (AF) – Heart Rhythm Society Guidelines

- **Paroxysmal**: Recurrent (≥ 2) atrial fibrillation episodes that terminate spontaneously within 7 days.
- **Persistent**: Atrial fibrillation that is sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion.
- **Longstanding Persistent AF**: Continuous atrial fibrillation of greater than 1 year duration.
- **Permanent**: Atrial fibrillation in which cardioversion has failed or not been attempted.

BLEEDING

- **Minor**
  Any overt*, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life-threatening bleeding.

- **Major**
  Overt bleeding either associated with a drop in the hemoglobin of ≥3.0 g/dl** or requiring transfusion of ≥3U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding.

- **Extensive**
  Overt source of bleeding with drop in hemoglobin of ≥ 4 g/dl or whole blood or packed RBC transfusion ≥ 4U within any 24-h period, or bleeding with drop in hemoglobin of ≥ 6 g/dl or whole blood or packed RBC transfusion ≥ 4 U (Overt bleeding plus hemoglobin drop ≥ 5 g/dl, cardiac tamponade, Bleeding requiring surgical intervention for control) excluding dental/nasal/skin/hemorrhoid)), OR Bleeding requiring IV vasoactive agents within 30 days of the procedure.

- **Life-threatening**
  Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intra- muscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.

- **Fatal**
  Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.

*"Overt" bleeding is defined by any of the following criteria being met: Reoperation after closure of sternotomy for the purpose of controlling bleeding; chest tube output >2 l within any 24-h period, >350 ml within the first post-operative hour, ≥250 ml within the second post-operative hour, or >150 ml within the third post-operative hour; or visible bleeding from the vascular system either at or remote from the access/surgical site.

**Adjusted for the number of units of blood transfused (1 U packed red blood cells or whole blood is equivalent to 1 g/dl hemoglobin).

DEATH (ALL-CAUSE MORTALITY)

A. Cardiovascular mortality

Any of the following contributing conditions:

- Heart failure (subclassified into left ventricular vs. right ventricular dysfunction)
- Myocardial infarction
- Major bleeding
- Thromboembolism
- Stroke
- Arrhythmia and conduction system disturbance
- Cardiovascular infection and sepsis (e.g., mediastinitis and endocarditis)
- Tamponade
- Sudden, unexpected death
- Other cardiovascular
- Device failure
- Death of unknown cause (adjudicated as cardiovascular)

B. Noncardiovascular mortality

Any death in which the primary cause of death is clearly related to another condition:

- Noncardiovascular infection and sepsis (e.g., pneumonia)
- Renal failure
- Liver failure
- Cancer
- Trauma
- Homicide
- Suicide
- Other noncardiovascular

MAJOR DEVICE OR PROCEDURE RELATED SERIOUS ADVERSE EVENT

All Major Serious Adverse Events adjudicated as device or procedure related, as defined by modified MVARC including:

- Procedure or Device related Death
- Procedure or Device related Stroke
- Procedure or Device related Life-threatening bleeding (MVARC scale)
- Major vascular or access (index procedure) complications
- Major cardiac structural complications related or cause by device or procedure
- Procedure related Stage 2 or 3 acute kidney injury (includes new dialysis)
- Procedure related Myocardial infarction or coronary ischemia requiring PCI or CABG
- Procedure or device related severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure, treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for more than 48 h.
- Any device-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention including:

- Structural or Functional failure of the HARPOON device, introducer or artificial chords (ePTFE) requiring an intervention.
- Conversion to the Open Mitral Valve Surgery secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or Secondary to procedural complications (such as cardiac perforation, removal of an embolized artificial chords, injury to Aortic valve and so on)
- Device malpositioning (Artificial chords malpositioning) requiring intervention. Permanent deployment of **artificial chord(s)** in a location other than intended or movement of the artificial chords during or post deployment which requires an intervention.
- Artificial Chord detachment (used with HARPOON device) which requires an intervention
- Device fracture: a break, tear, perforation, or other structural defect in the artificial chords (housing, leaflet, and so on) resulting in device failure, resulting in recurrent MR symptoms, or requiring reintervention.
- Damage to the native mitral valve apparatus (damage to native chordae tendinae, Leaflets, Papillary muscles or Mitral annulus) requiring an intervention or conversion to Open Mitral Valve Surgery.
- Symptomatic or requiring intervention Device Thrombosis (any thrombos attached or near the artificial HARPOON implanted chords)
- Interaction with non-mitral valve intracardiac structures which requires intervention and
- Endocarditis (as diagnosed by modified Duke endocarditis criteria or evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy) which required a surgical intervention.
- Hemolysis (a presence of a leaflet perforation on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus increased haptoglobin and/or LDH levels; which lead to a surgical intervention.
- Other major device or procedure related SAEs.

MYOCARDIAL INFARCTION

MI After Transcatheter and Surgical Mitral Valve Replacement

Periprocedural MI (≤48 h after the index procedure)

- In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to ≥10 x of the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5 x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70 x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or ≥35 x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB.

- In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described.

Spontaneous MI (>48 h after the index procedure)
Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile URL (or ULN in the absence of URL) together with at least 1 of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads
- Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

MI associated with sudden, unexpected cardiac death
Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood

Pathological findings of an acute myocardial infarction

STROKE AND TIA

Stroke is defined as a focal or global neurological deficit lasting more than 24 h OR less than 24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death.

A disabling stroke includes any neurological deficit (for example partial visual field cut) with a modified Rankin scale score equal or more than 2 with an increase in equal 1 or more modified Rankin scale score category from individual's pre-stroke baseline at 90 days after stroke onset.

Stroke and Transient Ischemic Attack: Diagnosis and Classification

Diagnostic criteria

- Acute episode of a focal or global neurological deficit with at least 1 of the following:
  a. Change in the level of consciousness
  b. Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body
  c. Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

- In addition, there is no other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist.
  Patients with nonfocal global encephalopathy will not be reported as having had a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or cerebral MRI).

The neurological event type classification

- Stroke: duration of a focal or global neurological deficit ≥24 h OR <24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death
- TIA: duration of a focal or global neurological deficit <24 h and neuroimaging does not demonstrate a new hemorrhage or infarct

Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following

- Neurologist or neurosurgical specialist, or
- Neuroimaging procedure (CT scan or brain MRI)

Stroke/TIA etiology classification

- Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
- Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic

Stroke severity is further classified as

- Disabling stroke: an mRS score ≥2 at 90 days plus an increase in ≥1 mRS category from the pre-stroke baseline
- Nondisabling stroke: an mRS score <2 at 90 days or without an increase ≥1 mRS category from the pre-stroke baseline

Reference:

Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2; Endpoint Definitions A Consensus Document from the Mitral Valve Academic Research Consortium.
Stone, Gregg W. M.D., Adams David H. M.D., et al.
Journal of American College of Cardiology Vol 66, NO, 3, 2015
ISSN 0735-1097