Registry for the Harpoon Medical Device

Beating Heart Mitral Valve REPair with the HARPOON™ System: ReaL world outcomes from a multICenter observATional European registry (REPLICATE #2019-12)

NCT04393779

January 14, 2020

Beating Heart Mitral Valve REPair with the HARPOON™ System: ReaL world outcomes from a multICenter observATional European registry (REPLICATE)

CLINICAL INVESTIGATION PLAN (CIP)

Protocol Number: 2019-12

Version: A
Date: 14 January 2020

Registry 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	14 January 2020

2.0 PROTOCOL SIGNATURE PAGE

Registry Title:	**HARPOON™ System: ReaL world outcomes from a multICenter observATional European registry (REPLICATE)**
Protocol Number:	**2019-12**
Version:	**Rev. A**
Date:	**14 January 2020**

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 registry protocol and in accordance with the International Standard ISO 14155 (relevant sections), 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 registry. 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 Registry Protocol will be conducted in accordance with

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

In addition, the Registry 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 REGISTRY CONTACTS

3.1 SPONSOR AND REGISTRY CONTACTS

REGISTRY DIRECTOR	PROJECT MANAGER

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

3.2 REGISTRY OVERSIGHT

CLINICAL RESEARCH ORGANIZATION

3.3 CLINICAL SITES

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

4.0 PROTOCOL SYNOPSIS

Title:	HARPOON™ System: ReaL world outcomes from a multICenter observATional European registry (REPLICATE)
Protocol Number:	2019-12
Sponsor	HARPOON™ Medical, an indirect wholly owned subsidiary of Edwards Lifesciences Corporation
Design:	A single arm, prospective, multicenter, post-market, observational registry
Objective:	To collect data on the HARPOON™ Mitral Valve Repair System for use in patients with severe degenerative mitral regurgitation due to posterior leaflet prolapse.
Device:	HARPOON™ Beating Heart Mitral Valve Repair System
Population:	Patients who undergo mitral valve repair surgery with the HARPOON™ Beating Heart Mitral Valve Repair System as part of standard of care treatment for severe degenerative mitral regurgitation due to mid- segment posterior leaflet prolapse
Enrollment:	Approximately 150 implanted subjects, including up to 30 subjects enrolled after the HARPOON surgery (capped at 5 subjects per site)
Definition of Enrollment:	A subject is considered enrolled upon providing a signed informed consent
Registry Sites:	Up to 50 sites in Europe
Follow-up:	Clinical and imaging assessments at baseline/pre-procedure, procedure, discharge, 30 days, 1-year and annually thereafter through 5 years post-implant, per local standard of care
Outcome Measures:	Freedom from re-operation due to recurrent severe mitral regurgitation through 1-year post-implant
Statistical Analysis:	No planned statistical hypothesis testing will be performed within this REPLICATE Registry protocol. Descriptive and summary statistical analysis will be provided for baseline/pre-procedure, procedure and outcome variables.

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
EFS	Early Feasibility Study
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

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6.0 INTRODUCTION AND BACKGROUND

6.1 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 included in the Trial Master File and Investigator Site File.

6.1.1 REGULATORY STATUS

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

6.1.2 INDICATION FOR USE

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

6.1.3 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. 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 (IFU).

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

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):

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 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 via transapical access thereby obviating the need for open surgery and its risks.

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 patients left the operating room without the investigational device. One case was aborted before the Harpoon procedure and 2 cases were converted to standard of care (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.

6.2.1 SAFETY ENDPOINTS

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 as 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.

There were no reports of unanticipated adverse device effects.

6.2.2 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.

6.2.3 SECONDARY PERFORMANCE RESULTS

6.2.3.1 MITRAL REGURGITATION

Severity of mitral regurgitation (MR) was 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. At 2-year follow up, 65.8% (25/38) of patients had mitral regurgitation of mild or less, 26.3% (10/38) of patients had moderate MR and 7.9% (3/38) of patients had severe MR.

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.

6.2.3.2 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.

6.2.4 SUMMARY

The results of the EFS and CE Marking trials support the safety and performance of the HARPOON System. Patient follow-up is ongoing.

7.0 REGISTRY DESIGN

7.1 OBJECTIVE

The objective of this registry is to collect data on the HARPOON™ Mitral Valve Repair System for use in patients with severe degenerative mitral regurgitation due to posterior leaflet prolapse.

7.2 DESIGN

The design is a single arm, prospective, multicentre, post-market observational registry.

7.3 OUTCOME MEASURES

The key outcome measure is freedom from re-operation due to recurrent severe mitral regurgitation through 1-year post-implant.

7.4 NUMBER OF SUBJECTS

Approximately 150 implanted subjects, including up to 30 subjects enrolled after the HARPOON surgery (capped at 5 subjects per site) will be included in this registry.

8.0 REGISTRY POPULATION

The registry population will comprise of subjects (over 18 years of age) who undergo mitral valve repair surgery with the HARPOON™ Beating Heart Mitral Valve Repair System per the IFU as part of standard of care treatment for severe degenerative mitral regurgitation due to mid- segment posterior leaflet prolapse, and who are willing to participate in the registry and provide signed informed consent for the collection and use of their data.

8.1 SCREENING AND ENROLMENT

Subjects who are clinically suitable for treatment with the HARPOON System, as per the IFU, will be evaluated for inclusion in the registry.

Subjects who agree to participate must sign an Ethics Committee (EC)-approved informed consent and will be considered part of the enrolled population.

As outlined in section 7.4, up to 30 subjects may be enrolled after undergoing the HARPOON surgery, capped at 5 subjects per site. Subjects that have already been implanted with the HARPOON device will be asked to sign an EC-approved informed consent to enroll in the registry to allow collection of the data on their HARPOON surgery and data through 5 year follow-up.

A subject is considered enrolled upon providing a signed informed consent.

9.0 REGISTRY PROCEDURES AND SCHEDULE OF ASSESSMENTS

9.1 SCHEDULE OF ASSESSMENTS

Clinical and echocardiographic data available from routine clinical assessments will be collected for the following time points: Baseline/pre-procedure, Procedure, Discharge, 30 days, 1 year and annually through 5 years. It is expected that the institutions' standard-of-care for the management of patients undergoing mitral valve repair surgery will be aligned and consistent with established guidelines and recommendations and may include the assessments described below.

9.2 SCREENING EVALUATIONS AND PATIENT ELIGIBILITY COMMITTEE

All 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.

9.3 BASELINE/PRE-PROCEDURE EVALUATIONS

The following baseline and pre-procedure assessments, if conducted as part of the institution’s standard of care, will be recorded:

- Assessment of NYHA Heart Failure Class
- 3D Transoesophageal echocardiogram (TOE)
- Assessment of Medical History

9.4 TREATMENT/PROCEDURE ASSESSMENTS

9.4.1 PROCEDURE OVERVIEW:

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

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

9.4.2 POST-PROCEDURE FOLLOW-UP ASSESSMENTS

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

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 pre-discharge testing as per hospital standard of care, which may include a comprehensive pre-discharge TTE.

Subject follow-up: Follow-up visits at 30 days, 1 year and annually through 5 years may be conducted in person (preferred) or via telephone interview, to minimize patient attrition, as per institution's standard of care. It is important that follow-up visit schedule be maintained as closely as possible for all subjects. Edwards recognizes that subjects may not be able to complete all scheduled follow-up at precisely the date required, and therefore, a period of time in which each visit could be completed is indicated in Table 1.

In the event that study personnel learn of a subject's hospitalization or re-operation outside the study center, the center should make every effort to obtain copies of reports or results based on tests (e.g.,

echocardiogram) and/or procedures performed on the study subject.

The following assessments, if conducted as part of the institution's standard of care, will be recorded through 5-year follow-up:

- Transthoracic echocardiogram (TTE)
- SAEs that results in a death, device-related events and device deficiencies/device malfunctions
- Assessment of NYHA Heart Failure Class (at 1-year follow-up only)

Table 1 summarizes the data that will be collected at each time point, per the local standard of care.

Table 1 - Data Collection Schedule

	Baseline/ Pre-Procedure	Procedure	Discharge	30 Days[1, 2] (+14 days)	1 Year[1] (+/- 30 days)	2-5 Years[1] (+/- 45 days)
Informed Consent	X					
Medical History	X					
TOE	X	X				
TTE[3]			X	X	X	X
NYHA Functional Class	X				X	
SAE that results in a death, ADE, SADE, USADE, device deficiency and device malfunction assessment[4]	X[5]	X	X	X	X	X

[1]All follow-up dates will be calculated from the date of the implant procedure. Follow-up visits may be conducted in person (preferred) and via telephone.
[2]Enrolled subjects for whom the implant procedure was prematurely aborted, 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 registry.
[3]TTE should be performed at 30 days, 1 year and annually through 5 year follow up or per local standard of care if TTE frequency or requirements are different from study schedule.
[4]Safety event reporting will start at the time of enrollment, i.e. subject providing a written informed consent, through 5-year follow-up.
[5]Only SAE that results in a death is applicable for reporting at Baseline/Pre-Procedure time point.
Abbreviations: ADE=adverse device effect; NYHA=New York Heart Association; SADE=serious adverse device effect; SAE=serious adverse event; TOE=transesophageal echocardiography; TTE=transthoracic echocardiography; USADE=unanticipated serious adverse device effect.

9.5 REGISTRY EXIT CRITERIA AND PROCEDURES

The reason for subject's exit from this registry will be documented on the appropriate electronic case report form (eCRF) and in the medical records for each subject.

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

- Device attempted but not implanted
    - Enrolled subjects for whom the implant procedure was prematurely aborted (e.g., entered operating room and anesthesia induced, but 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 registry.
- 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 registry.
- Completion per clinical investigation plan (CIP)

- Withdrawal
    - Subject Withdrawal: The subject may voluntarily withdraw from this registry 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 registry. Circumstances under which the Sponsor can suspend or stop this registry include, but are not limited to, low enrolment or new information regarding safety or device performance.
- Death
- Lost to follow-up
    - If a subject cannot be reached for at least two (2) consecutive follow-up visits.

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.

A subject who has been withdrawn from the registry will not be replaced.

9.6 DEATH AND SURGICAL VALVE INTERVENTION

9.6.1 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 registry electronic data capture (EDC) system.

9.6.2 SURGICAL VALVE INTERVENTION

In the event of device explant or surgical intervention, every effort should be made to obtain a copy of the procedure notes as well as any accompanying imaging data (i.e. CT, echo). Information on the cause of explant/surgical intervention will be determined by the investigator(s) and reported in the registry 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 registry. Effort should also be made to return any explanted 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 STATISTICAL METHODS

The analysis population will consist of the subjects who were enrolled and undergone a mitral valve repair surgery with the HARPOON System, regardless of procedure outcome. The analysis population excludes any subjects who signed the registry consent but were exited from the study prior to the procedure.

There is no planned statistical hypothesis testing within this REPLICATE Registry protocol. Descriptive and summary statistical analysis will be provided for baseline/pre-procedure, procedure and outcome variables.

11.0 SAFETY REPORTING

Safety event reporting to the sponsor is the Investigator's responsibility and will start at the time of enrolment and will continue through the duration of the registry.

The following critical safety events will be collected in this registry:

- SAEs where the outcome is death, and
- Device-related events/deficiencies.

These events will be recorded in the EDC system by the Clinical Study Coordinator (or designated site personnel). If the EDC system is not accessible, the event should be reported to the sponsor by using the following e-mail address: **REPLICATE-Safety@edwards.com**. Note: the event(s) will still need to be recorded in the EDC once the system is functional.

All the information related to the reported events, such as an awareness date, start and stop dates, description of event, seriousness, action taken and outcome, and relatedness to the HARPOON System procedure and device, will be assessed and recorded in the EDC system in a timely manner by the site. Whether an event meets the definition of serious or device-related will be determined by the registry investigator using the ISO 14155 definitions (see **Table 2)**. Relatedness of the event to the HARPOON System device will be determined by the investigator by using the causality categories listed below.

All relevant source documentation for reported events should be forwarded to Sponsor Safety Department via email **REPLICATE-Safety@edwards.com.** Source documentation must be redacted to remove identifiable references to the patient prior to submission to Sponsor.

Sponsor's Surgical Safety Team will review all reported events as per applicable regulatory requirements and Sponsor's internal standard operating procedures, including vigilance assessment and reporting to Edwards Complaint Handling or Regulatory Affairs groups who performs appropriate reporting to Regulatory Authorities, if applicable and per national legislation.

Local safety reporting to ethics committees will be completed, as required. Events will be collected and reported through 5 years post-procedure.

11.1 DEFINITIONS OF DEVICE-RELATED ADVERSE EVENTS AND DEVICE DEFICIENCIES

Table 3 below includes all event definitions as per ISO14155. Please note that for this registry, only the following events will be reported on the eCRFs:

- Adverse device effect (ADE)
- Serious adverse device effect (SADE)
- Unanticipated serious adverse device effect (USADE)
- SAE that results in a death
- Device deficiency/device malfunction

Table 2: Adverse Event Definitions (ISO 14155)

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:
	• 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.

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 above.
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.

Term	Definition
	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.
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 with its intended purpose when used in accordance with the instructions for use (IFU) or CIP.
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 RELATEDNESS OF REPORTED EVENT

Relatedness of the event to the procedure or the HARPOON System device will be evaluated by the investigator.

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

- Not related
- Related

11.3 REPORTING ADVERSE EVENTS

11.3.1 REPORTING BY THE INVESTIGATOR

As outlined above, reporting of applicable adverse events to the sponsor is the Investigator's responsibility and will start at time of enrolment and will continue until closure of the registry follow-up at 5 years post procedure or until a subject exits the registry.

The investigator shall notify the sponsor immediately and **no later than 3 calendar days** after the investigator or designated site personnel has become aware of an SAE that results in a death, SADE, USADE or device deficiency/device malfunction by completing the Adverse Event eCRF, or the Device Deficiency eCRF. Non-serious ADE should be reported to the sponsor as soon as possible upon the investigator or designated site personnel becoming aware of the event.

11.3.2 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 event reporting to the Ethics Committees according to the relevant local regulatory requirements, and to any other regulatory body, as required.

11.3.3 VIGILANCE REPORTING

Vigilance requirements apply and the site is required to report incidents and complaints as per the institution's procedure.

12.0 RISKS AND BENEFITS

Patients participating in this registry will undergo mitral valve repair surgery with the HARPOON System as part of their standard-of-care treatment for severe degenerative mitral regurgitation due to mid-segment posterior leaflet prolapse. There are potential risks related to the mitral valve repair surgery and the HARPOON System. These risks as well as product handling and implant procedure guidance are provided in the IFU.

No registry-specific procedures will be performed. The risk to the patient participating in the registry is a potential loss of confidentiality (see **Section 14.2** for more information).

Information gained from this registry may be of benefit to other people with the same medical condition in the future.

13.0 REGISTRY CONDUCT AND DATA MANAGEMENT

13.1 PROTOCOL DEVIATIONS

Each deviation from the protocol must be documented with the date and reason for the deviation and reported to Edwards as soon as possible, and to the EC per local guidelines and regulations.

13.2 REGISTRY CONDUCT, TRAINING, AND CONFIDENTIALITY

The registry will be conducted in accordance with the applicable regulations and guidelines as set forth in Section 14 of this protocol. The registry investigators are responsible for obtaining the appropriate regulatory approvals (ethics committee and, where applicable, Competent Authority approval) prior to initiation of the registry. The Investigator provides current copies of the registry protocol to all sub-Investigators or other staff responsible for registry conduct.

13.2.1 SITE INITIATION AND TRAINING

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

Training for each registry team member is documented on a Training Log. A Delegation of Authority Log is completed at each site for each staff individual designating which specific clinical registry related tasks may be performed. The delegated tasks will determine the training requirements for each member of the registry site staff.

New registry team members may be trained by previously trained personnel on the registry protocol and procedures.

Upon completion of site initiation, site will not be activated until the surgeons who will be using the HARPOON System have completed the required study-specific training. Documentation of that training must be retained in the registry regulatory binder.

13.2.2 HARPOON SYSTEM TRAINING

Edwards has established a training program for the surgeons who will be using the Harpoon System. This training program is designed to provide the surgeons with the information and experience necessary to

control user-associated risks when the device is used in accordance with the IFU. Surgeons participating in the registry will be trained on device use through didactic, practicum training, and proctoring.

13.2.3 SUBJECT AUTHORIZATION AND CONFIDENTIALITY

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

13.2.4 INVESTIGATOR CONFIDENTIALITY

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

13.3 DOCUMENTATION REQUIREMENTS

13.3.1 SOURCE DOCUMENTS

Clinical regulations require that Investigators maintain information in the subject's medical records that corroborate data collected on the eCRF.

To protect subject confidentiality, the subject's name must not appear anywhere on the imaging media sent to registry Sponsor. 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.

13.3.2 REGISTRY DOCUMENTS

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

- Investigator and site training to the protocol (Individual/Group Training Log)
- Authorized registry site personnel (Individual/Group Delegation of Authority)
- Subject consent and screening (Screening and Enrolment Log)

During the course of the registry, all significant correspondence regarding the registry must be maintained in the regulatory binder provided by the registry Sponsor. Significant e-mail correspondence may be archived electronically on CD/DVD. The regulatory binder must be made available for possible audits.

13.4 DATA MANAGEMENT

This registry will use a secure, password protected electronic data capture (EDC) system accessible via the Internet. A unique Subject ID will be assigned for each subject enrolled in the registry. All pertinent data will be entered by the registry site into the eCRFs.

Data review by Edwards personnel (or designee) will occur remotely. Data discrepancies will be queried and resolved through the EDC system.

The site Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and provide his/her electronic signature on the appropriate eCRFs at regular intervals during the conduct of the registry, as requested by Edwards. If changes are made to previously signed-off data, a new electronic signature will be required to acknowledge/approve the changes.

13.5 MONITORING

On-site monitoring will not be conducted by Edwards Lifesciences personnel (or designee) for data reported in this registry.

13.6 DATA AND DOCUMENT RETENTION

Registry-related correspondence, subject records, consent forms, and source documents are to be maintained on file by each participating site. The registry 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 registry must be maintained for no less than a period of two (2) years (or per local requirements) after registry closure and submission of the final report to the EC, or longer, as dictated by local regulations.

13.7 REGISTRY PROTOCOL AMENDMENTS

Changes in the protocol affecting the registry outcome are made only by written amendment agreed upon by the registry Sponsor, the applicable regulatory agency, and if pertinent, the EC. As appropriate, the registry 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 registry Sponsor **within five (5) business days.** Any major revisions to the protocol, must be approved by the Sponsor and the EC.

13.8 REGISTRY COMPLETION OR TERMINATION

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 registry master file.

Edwards Lifesciences reserves the right to terminate the registry at any stage for scientific, administrative or regulatory reasons, and reasons related to protection of subjects. Investigators, ECs/IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of registry termination.

13.9 PUBLICATIONS

All information related to the registry is considered confidential and remains the sole property of Edwards Lifesciences. 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 registry. Publication or presentation of the overall clinical registry results and/or site-specific results requires prior written approval of Edwards. If Edwards approves the publication or presentation of the overall clinical registry results and/or registry 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.

14.0 STATEMENTS OF COMPLIANCE AND CONFIDENTIALITY

14.1 APPLICABLE REGULATIONS AND GUIDELINES

This registry will be conducted in compliance in accordance with the ethical principles that have their origin in the Declaration of Helsinki as well as with the relevant sections of the ISO14155 and any regional or national regulations as appropriate.

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 registry.

The registry shall not begin until the required approval/favourable opinion from the EC. Any additional requirements imposed by the EC shall be followed.

14.2 DATA PROTECTION AND PATIENT CONFIDENTIALITY

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

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 registry.

With respect to data protection and patient confidentiality, Sponsor, Institution and all Registry 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.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that this clinical registry is conducted according to the Clinical Trial Agreement, clinical investigation plan (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 registry at each site.

The Investigator is responsible for ensuring that informed consent is obtained from all subjects prior to any data being collected. Safety reports to the local ethics committee (EC) will be submitted, as required. 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 registry 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.

14.4 SPONSOR RESPONSIBILITIES

The Sponsor is responsible for ensuring that this registry will be conducted in compliance with all applicable local and European regulations. The Sponsor must ensure that EC approval is obtained and remains current. The Sponsor is responsible for the conduct and administration of this clinical registry.

These responsibilities include maintaining regular contact with each registry site to ensure compliance with this Clinical Investigational Plan and verify that data are reported in a timely manner.

This registry 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.

ATTACHMENT A – SUGGESTED DEFINITIONS

Modified MVARC definition are suggested for the event reporting purpose.

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 RELATED SERIOUS ADVERSE EVENT

All Major Serious Adverse Events reported as device related, as defined by modified MVARC including:

- Procedure or Device related Death
- Device related Stroke
- Device related Life-threatening bleeding (MVARC scale)
- Major vascular or access (index procedure) complications caused by the device
- Major cardiac structural complications related or caused by the device
- Device related myocardial infarction or coronary ischemia requiring PCI or CABG
- 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 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

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 non-stroke 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 non-focal 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.

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