Safety and Performance Study of the Harpoon Mitral Valve Repair System

NCT03285724

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Protocol Title: Safety and Performance study of the Harpoon Medical Device in patients with degenerative mitral regurgitation

Protocol Number: HMEFS -2000

Version: 00a dated 12Oct2016

Sponsor:

[redacted]

Monitor:

[redacted]

European Authorized Representative:

[redacted]

CONFIDENTIALITY STATEMENT

This study is confidential in nature. All information related to this study is considered proprietary and should not be made available to those not directly involved in this study. Authorized recipients of this information include investigators and co-investigators, other health care personnel necessary to conduct the study and Ethical Committees

The above personnel provided with data from this study are hereby informed of its confidential and proprietary nature. Release of this data to individuals other than those listed above requires the prior written permission of Sponsor.

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I. PRIMARY CONTACTS

Sponsor:		**Monitor:**
[redacted]		[redacted]
European Authorized Representative:		
[redacted]		
Principal Investigator(s)		(*Protocol Signature pages are provided separate to this protocol)*
[redacted]		[redacted]
[redacted]		

II. STUDY SUMMARY

Title:	Safety and Performance study of the Harpoon Medical Device in patients with degenerative mitral regurgitation
Protocol Number:	HMEFS-2000 Ver 00a
Design:	This is a prospective, single arm, nonrandomized, early feasibility study to evaluate the safety and performance of the Harpoon Medical Device.
Study Duration:	Projected enrollment of first patient December 2016 Projected exit of final patient: December 2019
Primary Objective:	The primary objective of this study is to evaluate the safety and performance of the Harpoon Medical Device.
Patient Population:	Patients with “Severe” mitral regurgitation as a result of posterior, bi-leaflet or anterior prolapse.
Sample Size:	Up to twenty (20) patients in PL will be enrolled.
Number of Sites:	Krakow will be the only center participating in this study.
Treatments:	Up to eight (8) pairs of ePTFE cords may be placed in the anterior and/or posterior mitral valve using the Harpoon Medical Device in order to establish effective coaptation of the mitral leaflets.
Endpoints:	**Primary Performance Endpoints**: To demonstrate that the Harpoon Medical Device performs as designed and can successfully implant one or more ePTFE artificial cords on either the anterior, posterior, or both leaflets of the mitral valve via a small left thoracotomy on the beating heart and reduce mitral regurgitation from “severe” to less than or equal to “moderate” at the conclusion of the procedure and at 30 days post-procedure. **Secondary Performance Endpoints:** Severity of mitral regurgitation at 6 months, 12 months and 24 months follow-up shall be tracked and recorded **Primary Safety Endpoints**: Procedure freedom from Serious Adverse Events (SAEs) during the procedure, at discharge, and at 30 days follow-up shall be tracked and recorded. Rates are expected to be not significantly worse than conventional mitral valve surgery. **Secondary Safety Endpoints** Freedom from Serious Adverse Events (SAEs) at 6 months, 12 months and 24 months follow-up shall be tracked and recorded

Inclusion Criteria:

- Age ≥ 18 years
- Patient referred for mitral valve surgery
- Presence of severe MR as read on an echocardiographic study performed within 60 days prior to procedure.
- Estimated post-ePTFE cordal implantation coaptation surface is adequate in the judgment of the operating surgeon and the patient eligibility committee
- Degenerative mitral valve disease associated with anterior, bileaflet, or posterior leaflet prolapse
- 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
- Women of child-bearing potential have a negative pregnancy test

Exclusion Criteria:

- Age < 18 years
- Infective endocarditis
- History of Mediastinal Radiation
- Inflammatory (rheumatic) valve disease
- Requirement for concomitant cardiac surgery (e.g., coronary artery bypass grafting (CABG), aortic valve surgery, etc.)
- Symptomatic coronary artery disease
- Cardiogenic shock at the time of enrollment
- ST segment elevation myocardial infarction requiring intervention within 30 days prior to enrollment
- Evidence of cirrhosis or hepatic synthetic failure
- Pregnancy at the time of enrollment (women of child bearing age should have negative pregnancy within 14 days of surgery)
- Severe pulmonary hypertension (PA systolic pressure > 70 mmHg)
- Previous cardiac surgery, or surgery on the left pleural space
- Left ventricular, atrial or appendage thrombus
- Severely calcified mitral leaflets
- Recent stroke (< 6 months) with permanent impairment
- EuroScore (for mitral valve repair) > 8%
- Patients with contraindications to Transesophageal echocardiography
- Severe left or right ventricular dysfunction
- NYHA Class IV
- Renal insufficiency CKD stage 3b or worse (GFR < 45 ml/min/1.73 m^2)
- Patient is participating in another clinical study for which follow-up is currently ongoing. (Co-enrollment in an investigational device or interventional study)
- Patient with non-cardiac co-morbidities and life expectancy < 1 year

- Patient has a condition or conditions that, in the opinion of the Investigator, preclude participation, including willingness to comply with all follow-up procedures

Follow-up: The estimated enrollment period is 24 months, and all patients will have follow-up visits at 30 days, 6 months, 12 months and 24 months after implantation.

III. BACKGROUND AND RATIONALE

Mitral Regurgitation, Transapical mitral valve repair, and the Harpoon Medical Device

Patients with Mitral Regurgitation may benefit from treatment with this device. Mitral valve disease is the most common valvular heart disorder[i]. Nearly 4 million Americans are thought to have severe mitral valve regurgitation ("MR"). 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 surgical mitral valve repair restores mitral valve competence, abolishes volume overload on the left ventricle, improves symptom status and prevents adverse left ventricular remodeling.

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 patients with ischemic or idiopathic MR (the motion of the normal mitral valve leaflets is restricted by the enlarged ventricle, both of which lead to ineffective apposition of the anterior and posterior mitral valve leaflets and failed valve closure and regurgitation.

Two-thirds of all mitral valve repair procedures in North America are performed on patients with degenerative MR. The case mix is estimated to be similar in the European Union (EU). Mitral valve repair that requires open cardiac surgery, aortic manipulation and cardio-pulmonary bypass is the most common method to treat MR. There are also other less invasive devices currently on the market in the US and the EU that are considered alternative treatment options for MR. The follow is a summary of the current treatment options available to replace ruptured or elongated cords and reduce MR:

There are alternate treatments available to replace ruptured or elongated chordae tendineae and reduce MR. However, there is no currently effective medical therapy that cures MR, and the alternate procedures to repair the mitral valve are generally more invasive and associated with greater morbidity and/or less effective repair of the mitral valve. The current technologies available to address the structural defects of MR include:

- Open heart operations to repair or replace the mitral valve. Open cardiac mitral valve operations require a large chest incision (either sternotomy or thoracotomy), cardiopulmonary bypass, aortic manipulation and cardioplegic cardiac arrest. Mitral valve repair often requires a mitral annuloplasty ring and is performed with leaflet resectional techniques (Carpentier) or nonresectional techniques using ePTFE cords placed under direct vision. Mitral valve replacement is performed by replacing the native diseased valve with a mechanical prosthesis or a bioprosthesis. In either event, a large incision, cardio-pulmonary bypass and extensive surgery are required. Moreover, lifelong anticoagulation is required post-operatively.

- In 2008, Evalve received a CE mark for the MitraClip Transcatheter Mitral Valve Repair in the European Union. Shortly thereafter, the company was acquired by Abbott Labs. In 2013, Implantation of MitraClip does not involve open-heart surgery, but mimics a surgical method of edge-to-edge valve repair (the Alfieri technique) where the mitral valve leaflets are clipped together with the device instead of being sutured together. The MitraClip Transcathether Mitral Valve Repair Clip delivery system (MitraClip CDS) consists of implant catheters and the MitraClip device. The device is a permanent implant that attaches to the mitral valve leaflets. The MitraClip CDS is intended to treat patients with significant symptomatic degenerative mitral regurgitation with MR ≥ 3+ who have too high a risk for surgery. While the MitraClip

does improve apposition of the mitral leaflets, the apposition does not mimic the natural pattern of valve movement, and the device has not been widely adopted.

- In 2013, Neochord released a CE marked, Class III medical device to the European Union as a minimally invasive procedure that is performed on a beating heart to replace cords that have become elongated or ruptured. Neochord does not involve open-heart surgery. It mimics the surgical method of suturing replacement cords to the free-edge of the mitral valve leaflet. The NeoChord procedure is performed transapically on the beating heart via a thorocotomy between the ribs. Using echocardiographic guidance, the NeoChord DS1000 places individual cords on the prolapsed leaflet using an expandable jaw to grasp the leaflet and insert the chord. When a sensor on the DS100 jaws confirms that the leaflet has been adequately captured the surgeon deploys the ePTFE suture into the leaflet. The device is then removed and the distal end of the suture is secured to the epicardium with pledgets. Correct length of the suture is determined by using real time echocardiographic guidance to observe improvement in mitral valve regurgitation in the beating heart. Data from the TACT study (NCT01777815) used to support the CE mark showed a high procedural success and demonstrated that off-pump transapical implantation of artificial chordae to correct MR is technically safe and feasible. NeoChord is currently conducting a TACT Post-Market Surveillance Registry (NCT01784055) to evaluate patients who had at least one cord placed using the DS1000 System AND reduction in mitral regurgitation ≤ 2+ at the time of the procedure. NeoChord is not currently available in the US. The NeoChord system is currently being used to treat patients in 18 hospitals in 8 country's which include TACT registry and non-registry centres in Europe. Over 250 patients have been treated to date. Mid-term outcomes in treating severe MR are very promising.

Although these procedures are available to cardiac surgeons in the US and/or EU, there is still a need for additional minimally invasive treatment options for patients suffering from MR. Ideally, these treatments should avoid cardio-pulmonary bypass and open heart surgery. They should be minimally invasive, technically simple.

DEVICE DESCRIPTION

The Harpoon Medical Transapical device is intended to be used to reduce the degree of degenerative mitral regurgitation by delivering and anchoring ePTFE cords to the affected mitral valve leaflet(s) in a beating heart in patients with anterior, bi-leaflet or posterior prolapse. The device is intended to be a Single Use Device, used in a surgical operating suite or equivalent setting. Harpoon Medical has developed a novel small-diameter (< 3 mm) rigid linear delivery system (TSD-5) using a needle wrapped with ePTFE in a pre-formed knot configuration. The device delivers replacement ePTFE cords using a valved introducer (TAV-5) and Transesophageal echocardiography (TEE). To deploy the pre-formed knot on the atrial side, the TSD-5 is actuated to advance the needle and pre-formed knot through the leaflet. The TSD-5 then retracts the needle, leaving the pre-formed knot on the atrial side of the leaflet. After deployment, the TSD-5 is withdrawn from the TAV-5, exposing the replacement cords. The replacement cords are adjusted under real-time TEE to optimize the surface of coaptation between leaflets before they are secured to an ePTFE pledget on the epicardium.

The Harpoon Medical Device consists of two parts: 1) the delivery system (TSD-5) – Figure 1 and 2) the valved introducer (TAV-5) – Figure 2. Both items are essential for the proper delivery of the suture(s) in the mitral valve leaflet to eliminate or reduce Mitral Valve Regurgitation (MR).

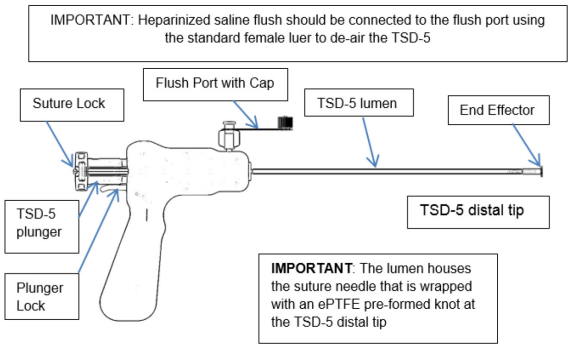

Figure 1 - Delivery System (TSD-5)

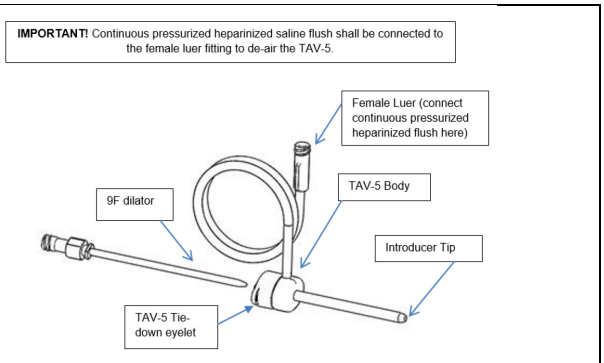

Figure 2 - Valved Introducer (TAV-5)

The manufacturer of the study device is Harpoon Medical, Inc. having an address of 351 West Camden Street Suite 801 Baltimore, MD 21201 USA.

The purpose of this study is to evaluate the safety and performance of this Harpoon Medical Device.

Devices used in the clinical investigation will be traced according to their lot number. The Lot numbers are coded YY-WWW, where the YY is “16” for those devices sterilized in 2016 and DDD signifies the Julian calendar day of the associated year.

A detailed device description is provided in the Investigator’s Brochure in section 1.2 and the Instructions for Use for the system.

SUMMARY OF PRECLINICAL STUDIES

Harpoon has completed enrollment (n = 13) in an Early Feasibility Study across two locations in Poland and has begun enrolling patients in a larger randomized study across multiple countries in Europe to support CE Mark. All thirteen patients enrolled in the EFS had severe degenerative MR and will be evaluated for two years with follow-up visits at 30 days, 6 months, 1 year and 2 years. All echocardiographic studies are graded by an independent core laboratory based on the American Society of Echocardiographer (ASE) Guidelines. An interim report of the Early Feasibility Study based on data available as of December 31, 2015 was published by Gammie et al. in *Circulation* on July 19, 2016. There was 100% procedural success in the thirteen patients enrolled in the EFS and zero procedural and perioperative mortality. Between 3 and 5 chords were implanted in each patient. The average introducer time (the time TAV-5 is inserted into the left ventricle) was 38 minutes and the average skin-to-skin procedure time was 110 minutes. After the ePTFE suture pairs were implanted and secured at the epicardial site; anterior-posterior mitral leaflet coaptation was restored and the severity of MR was significantly reduced. Ten of the EFS patients had None/Trace MR and the balance had Mild MR at the conclusion of the procedure.

As of August 31, 2016, all of the eligible patients in the EFS have completed their thirty day and six month follow-up visits, and 6 patients have completed one-year follow-up. 9 of the 13 patients in the EFS had none/trace or mild MR at six months and 2 were graded as moderate MR and were asymptomatic. The result observed at six months has been stable in each of the six patients who have completed their one-year follow-up visit. Among 6 patients with one-year follow-up, 3 had none/trace MR, 1 had mild, and 2 had moderate MR and were asymptomatic. There has been no mortality, no procedural conversion to open-heart surgery, no stroke, no

renal failure, no myocardial infarctions, no blood transfusions and no new onset atrial fibrillation in patients enrolled in the EFS. There were two reoperations for delayed tamponade on post-operative day 5 and 13. Both patients recovered rapidly and were discharged in excellent condition. Two patients required re-operation for recurrent MR. In one patient an ePTFE cord came untied at the apical pledget. The other patient had recurrent MR as a result of a ruptured native anterior leaflet cord. Both patients underwent a successful on-pump mitral valve operation (post-operative day 72 and 231 respectively) and recovered without incident. To date the EFS has generated 4,651 total “patient days” (patients implanted * days implanted) equal to 12.7 years and 16,843 “cord implant days” (total number of cords implanted * days implanted).

Harpoon Medical has begun enrollment in the CE Mark Study, and while the data is not complete yet, the preliminary results appear to be consistent with the Early Feasibility Study. As of August 31, 2016, a total of 92 ePFTE cords have been implanted in 24 patients across the EFS and CE Mark studies. Harpoon has a total of 5,465 patient implant days equal to 15.0 years and 19,964 cord implant days which is equal to 54.7 years of experience with Harpoon chords implanted in a human heart. The Harpoon ePTFE bulky knot anchoring mechanism has proven durable to date with no cords pulling out of a leaflet after implantation in the operating room. In summary, the data collected to date supports the conclusion that the Harpoon Medical Delivery System (TSD-5) and the Valved Introducer (TAV-5) can be used safely on degenerative MR patients.

Since this study will use the same device, as was studied in the first Early Feasibility Study and the CE Mark study to investigate the feasibility of the use of the device for anterior, bi-leaflet and posterior degenerative mitral regurgitation, and since there has been no mortality, no stroke, no renal failure, no myocardial infarctions, no blood transfusions and no new onset atrial fibrillation for the enrolled patients, the expected outcomes for this study should be similar.

POTENTIAL BENEFITS

It is anticipated, that the Harpoon Medical Device will provide advantages over current surgical interventions including:
1) a small minimally invasive incision
2) no sternotomy,
3) no cardiopulmonary bypass,
4) no aortic manipulation,
5) a direct path to the valve plane,
6) performed on a beating heart,
7) real-time TEE-guided ePTFE cordal length adjustment and
8) less complicated procedure that is teachable and adoptable.

The only intracardiac implant associated with the Harpoon Medical Device is an ePTFE suture, which has a 25+ year history of safety in conventional mitral valve repair procedures. Moreover, the Harpoon approach is unlikely to compromise subsequent traditional open-heart mitral valve repair or replacement procedures.

POTENTIAL RISKS

There are risks associated with our protocol. The Harpoon Medical Device is an “Investigational Device” that does not bear a CE Mark. It is not available for market into the EU. The study uses minimally invasive surgical techniques to repair/replace the native chordae in a human heart. The discomforts and risks that are equivalent to what is expected from similar cardiac procedures

performed through the chest wall on a beating heart to repair the mitral valve (i.e., localized pain, discomfort at the incision site(s) and the risks of bleeding, injury to the myocardium and injury to the mitral valve).

A detailed risk analysis has been completed in accordance with ISO 14971:2012. The conclusions from the risk assessment is that when the Harpoon Medical Investigational device is used in accordance with the Indications for Use of the device, it will not present risks to the patient that are not able to be mitigated either through the device design controls, the contraindications, warnings and operator training. All risks that were evaluated, analyzed or reviewed assured that the risk of the TRACER procedure using the Harpoon Medical Device is as low as possible to for the user or the patient. The following categories of procedure and device related functional risk were analyzed as part of the risk analysis:

A) Ability to Access – the risks assessed are associated with the patient type, the access to the heart using a left thoracotomy and the ability to complete the procedure without a conversion to open repair. The key risks evaluated are:
   - Conversion to open repair of the mitral neochodae post-procedure
   - Excessive Blood loss through the valved introducer
   - Assembled components joints fail resulting in excessive blood loss
   - Ability to Access the Mitral Leaflet using a thoracotomy and the valved introducer to complete the procedure

B) Implant Integrity – the risks assessed are associated with the device performance and function and intended use to be able to implant one or more ePTFE cords to reduce mitral regurgitation. The key risks evaluated are:
   - The knot pulls through the leaflet after implant at the time of implant or post-implant
   - Damage occurs to previously deployed knots with the passage of subsequent devices through the valved introducer
   - The knot fails for form correctly resulting in reduced anchoring force on the mitral leaflet
   - The suture does not un-thread from the device resulting in catching and the knot pulls out during device withdrawal
   - The Mitral valve cordal repair construct fails due to fatigue
   - The Manufacturing joints fail causing the knot to form incorrectly resulting in low anchor forces or detached components
   - Post-Implant, the body fails to endothealise the ePTFE suture

C) Lack of Sterility - the risks assessed are associated with the device being marked as sterile and the device not delivered as sterile and results in cross-contamination or infection to the patient. The key risks evaluated are:
   - Breach of the sterile barrier on the packaging and contamination to the patient
   - Use of the device with an expired shelf life
   - Use of contaminated or unclean product, results in infection and/or contamination to the patient

D) Lack of Biocompatibility – the risks assessed are associated with the device or the ePTFE implant not being physiologically compatible with the patient. The key risks evaluated were:
   - Use of materials that are not physiologically compatible with the human body and tissues, results in the human body rejecting the ePTFE implant

All risk management was performed in accordance with BS EN ISO 14971: 2012 which primarily affects the Essential Requirements of the Medical Device Directive in accordance with 2007/47/EC and 93/42/EEC to assure that the risk is mitigated to the lowest possible risk. Contraindications and Warnings were placed in the labeling to exclude patients that are

identified in the Exclusion criteria of the Clinical Protocol. Cautions, Pre-Cautions and Important Notes are added to the Instructions for Use and the Surgeons Technical Guide as a means to reinforce risks that the surgeon should be aware of when performing the TRACER procedure.

All risks analyzed as part of the risk management process were able to be mitigated to a level as low as reasonable either through a design control, contraindication or warning in the Surgeon's Technical Guide or the Instructions for Use. Although not credited directly for any mitigation of risk, the Investigator Training program provides qualification of the investigators to perform the TRACER procedure. The pre-clinical testing and the Risk Analysis completed in accordance with ISO-14971 provides good confidence that the device when used in accordance with the intended use is a safe device for Patients who meet the inclusion criteria

MINIMIZATION OF RISKS

Measures which have been taken to minimize risks which include testing of materials and device configurations.

Measures which will be taken to minimize risks related to the study include:

- Selection of investigator(s) trained in performing this type of implant
- Investigator training by Harpoon Medical personnel or representative
- Well defined clinical investigation plan, including specific inclusion/exclusion criteria to enroll appropriate patients in the study
- Close patient monitoring during the device implant procedure and follow-up period by the investigator(s) and their associates
- Ongoing monitoring of study data and results by the study sponsor and sponsor's representatives
- Selection of patients in rigorous compliance with the clinical investigational plan

OPERATOR TRAINING AND EXPERIENCE

Each of the Principal Investigators AND any physician having an integral part in the procedure are required to complete an extensive training program in order to qualify them as Harpoon trained study doctors. The training program is focused on hands-on practical experience and an understanding of the philosophy of the Harpoon device and use in the clinical setting. The following is an overview of the Harpoon Clinical Therapy Training program that the on-site surgical team shall:

- Establish an understanding on how to identify patient's that are eligible for the Harpoon mitral valve repair procedure
- Establish an understanding of the intra-operative surgical and echo guidance techniques employed in the Harpoon procedure
- Be able to properly insert the Harpoon valved introducer (TAV-5) and deploy the Harpoon delivery system (TSD-5)
- Demonstrate suture titration techniques
- Understand post-operative care

Additionally, each of the PIs must also complete the several training exercises, prior to using the Harpoon device on any of the patient enrolled from their study sites. Once the surgical team has completed these training elements, they are considered to be a certified Harpoon center

IV. STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety and performance of the Harpoon Medical Device.

Study Hypothesis

Reduction in Mitral Regurgitation from “severe” to less than or equal to “moderate” at the conclusion of the procedure and at 30 days post-procedure.

Endpoints

Primary Performance Endpoints: To demonstrate that the Harpoon Medical Device performs as designed and can successfully implant one or more ePTFE artificial cords on either the anterior, posterior, or both leaflets of the mitral valve via a small left thoracotomy on the beating heart and reduce mitral regurgitation from “severe” to less than or equal to “moderate” at the conclusion of the procedure and at 30 days post-procedure.

Secondary Performance Endpoints: Severity of mitral regurgitation at 6 months, 12 months and 24 months follow-up shall be tracked and recorded

Primary Safety Endpoints: Procedure freedom from Serious Adverse Events (SAEs) during the procedure, at discharge, and at 30 days follow-up shall be tracked and recorded. Rates are expected to be not significantly worse than conventional mitral valve surgery.

Secondary Safety Endpoints Freedom from Serious Adverse Events (SAEs) at 6 months, 12 months and 24 months follow-up shall be tracked and recorded

Rationale for Endpoint selection

The primary and secondary performance and safety endpoints are the same endpoints as what was currently tested in the first Early Feasibility Study in PL and what is currently being tested in the CE mark study design. Our intent of this study and using these endpoints, if to further understand if the treatment of using the Harpoon Medical device for anterior, posterior and bi-leaflet prolapse can meet these endpoints.

V. STUDY DESIGN

This is a prospective, single arm, nonrandomized, early feasibility study to evaluate the safety and performance of the Harpoon Medical Device.

VI. STUDY POPULATION

NUMBER OF PATIENTS

Up to 20 patients in PL may be enrolled. The estimated enrollment period is 24 months, and all patients shall be followed for 30 days, 6 months, 12 months and 24 months after implantation in accordance with the Clinical Investigations schedule provided in Section VIII.

INTENDED USE

The Harpoon Medical Device is intended to be used by a trained medical professional. The device is designed to reduce the degree of mitral regurgitation by delivering and anchoring artificial chordae tendineae to the affected mitral valve leaflet(s) in a beating heart. The device is intended to be a Single Use Device, used in a surgical operating suite or equivalent setting.

INCLUSION CRITERIA

- Age $\geq$ 18 years
- Patient referred for mitral valve surgery
- Presence of severe MR as read on an echocardiographic study performed within 60 days prior to procedure.
- Estimated post-ePTFE chordae tendineae implantation coaptation surface is adequate in the judgment of the operating surgeon and the patient eligibility committee
- Degenerative mitral valve disease associated with anterior, bileaflet, or posterior leaflet prolapse
- 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
- Women of child-bearing potential have a negative pregnancy test

EXCLUSION CRITERIA

- Age < 18 years
- Infective endocarditis
- History of Mediastinal Radiation
- Inflammatory (rheumatic) valve disease
- Requirement for concomitant cardiac surgery (e.g., coronary artery bypass grafting (CABG), aortic valve surgery, etc.)
- Symptomatic coronary artery disease
- Cardiogenic shock at the time of enrollment
- ST segment elevation myocardial infarction requiring intervention within 30 days prior to enrollment
- Evidence of cirrhosis or hepatic synthetic failure
- Pregnancy at the time of enrollment (women of child bearing age should have negative pregnancy within 14 days of surgery)
- Severe pulmonary hypertension (PA systolic pressure > 70 mmHg)
- Previous cardiac surgery, or surgery on the left pleural space
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- Patients with contraindications to Transesophageal echocardiography
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- Renal insufficiency CKD stage 3b or worse (GFR < 45 ml/min/1.73 m^2)
- Patient is participating in another clinical study for which follow-up is currently ongoing. (Co-enrollment in an investigational device or interventional study)

- Patient with non-cardiac co-morbidities and life expectancy < 1 year
  Patient has a condition or conditions that, in the opinion of the Investigator, preclude participation, including willingness to comply with all follow-up procedures

VII. PATIENT ENROLLMENT

PRE SCREENING

Screening evaluations: All patients that are identified as potential candidates for the study shall undergo transthoracic echocardiography (TTE). This echo should have been performed within the two months preceding the patient's inclusion in the study.

A TEE will be performed at the referring doctor's request. Both the TTE and TEE are routinely performed in patients undergoing heart valve surgery.

If the patient is deemed to be a good candidate for the study, the investigator will ask him to sign the Echo PIC to release existing medical records to the Harpoon Patient Eligibility Committee (PEC) for review and evaluation for enrollment. These records include the screening evaluations (anonymized echocardiogram along with the limited medical information (age, vital signs)).

The PEC will provide the study site with a Pass or Fail for the patient being screened.

If the PEC determines a PASS for the patient under consideration, Harpoon Medical will validate the participation and the patient will be asked to sign the study informed consent and, once officially enrolled, will proceed to the pre-procedure/baseline evaluations.

If the PEC determines a FAIL for the patient, the patient will be referred back to the standard of care. If the patient data is not satisfactory for the PEC, the PI may request a new echo be completed if this falls under standard practice. This new echo will then be submitted to the PEC for re-evaluation. All data received by the PEC for this patient will be destroyed. Only data compiled in screening enrollment log will remain.

In any case, the PEC will provide the site with an MDDX number for each patient reviewed. The site will be asked to maintain a list of these numbers and the related patients. This information will be reported on a Screening and Enrollment log maintained in the study file on site. The MDDX number is composed of two digits for site number and two digits for patient number. Only one number will be given per patient and will remains the same if the patient is further enrolled.

INFORMED CONSENT

Patients who have been pre-screened and for whom the principal investigator feels would be a good candidate for inclusion in the Trial, will be asked to sign the study specific Ethics Committee (EC) approved Patient Information Sheet before any study-specific tests or procedures are performed. Enough time will be given to the patient (at least 24h) to read and understand the informed consent form and to consider participation in the clinical investigation.

The PI (or one of his co investigators specifically identified on the delegation log and authorized to do so) will answer all patients' questions and will clearly explain to the patients that even if they agree to participate in the study and sign the Patient Information Sheet, they can withdraw their

consent to participate at any time. They will continue to be followed and treated by the site as normal. The site personal will make sure also that the patients have understood what their participation means (visits and tests scheduled) and that even if they sign the consent they may not be eligible to participate if he/she fails additional eligibility criteria.

The Screening/Enrollment Log is maintained in the on-site clinical records located at the study site to document select information about candidates who pass or fail to meet the entry criteria.
In the case a patient does not want to participate to the study, the PEC will destroy the data transferred.

ENROLLMENT

Point of enrollment: a patient will be officially considered as enrolled after consent has been signed and dated by him/her. The patient will be followed until his/her study exit (study completed, withdrawal, lost to follow up, death). All the events will be registered from that date and until the patient leaves the study for one of the reason previously mentioned.

One original form will be kept on site (in patient's medical records) and one will be provided to the patient. The version kept on site will be reviewed by the clinical monitor during the monitoring visit to ensure that the correct version has been signed and that the consenting process has been respected.

The site staff will also make sure that the patient study participation is clearly indicated in patient's files.

PRE-PROCEDURE/BASELINE EVALUATIONS

Once the patient is officially enrolled for the Harpoon Medical study, a Physical Assessment will be performed. This includes:

- Vital signs
- 12-lead ECG
- Routine Laboratory assessment (including WBC count; Hemoglobin; hematocrit; platelet count; creatinine Level, INR)
- Additional Laboratory assessment (including Total Albumin, Total Bilirubin, BNP, NTproBNP)
- A chest radiograph (X-Ray)
- A serum pregnancy test for females with childbearing potential (age < 50 years) shall be completed within 14 days prior to the procedure
- In accordance with the hospital's clinical Standard of Care, a left heart catheterization (LHC) may be required for all patients >/= 45 years of age without risk factors and for any patient with symptoms of coronary artery disease
- Pulmonary Function Tests, when clinically indicated
- 6 Minute Walk test
- Quality of Life Assessment
- EUROscore assessment

The data from this physical assessment shall be recorded on a Case Report Form (CRF).

TREATMENT PROCEDURE/ASSESSMENTS

The procedural approach requires that the patient be administered a general (single lumen) endotracheal anesthesia with appropriate monitoring lines (e.g. arterial line) and heparinized saline to achieve an activated clotting time of ≥ 350 seconds. The patient should be placed in the supine position with elevation of the left hemithorax to 30°. Briefly, the procedure consists of performing a small left lateral thoracotomy incision overlying the left ventricular apex, opening the pericardium and selecting an insertion site on the epicardium for the Harpoon Medical device where a monofilament purse-string suture is placed to hold the Harpoon device introducer in place and reduce bleeding. Once the introducer is in place, the device is inserted and positioned adjacent to the mitral leaflet under TEE guidance and bulky suture knot is deployed to secure paired sutures in the leaflet. The paired sutures are brought outside the ventricle. Up to four (4) suture pairs may be placed, using a single valved introducer (TAV-5), to secure and align apposition between the anterior and posterior mitral leaflets. If more than four (4) suture pairs are required, the TAV-5 must be removed and reinserted for reuse, and then an additional four (4) suture pairs may be inserted. Once an adequate number of suture pairs are placed, the device and introducer are removed, and the suture pairs are tightened and secured to the exterior myocardium using pledgets for each suture pair. The thoracotomy should be closed, and chest tube(s) should be inserted, per hospital standard of care.

The details of the procedure a described thoroughly in the Harpoon Medical Device Instructions for Use.

If in the judgment of the operating surgeon, adequate MR reduction has not been achieved, or if for any other clinical reason, conversion to SOC mitral valve surgery via a median sternotomy shall be performed. This procedure may be performed at the time of the Harpoon Medical procedure or at a later date/time at the discretion of the operating surgeon.

FOLLOW-UP PROCEDURES/ASSESSMENTS

Post-procedure management: Standard hospital protocols for the management of patients after mitral valve surgery shall be followed. Unless other indications for anticoagulation are present, all patients shall receive only 325 mg/day low dose aspirin, beginning on arrival to the intensive care unit).

Discharge: All patients shall be discharged from the hospital at the discretion of the attending cardiac surgeon.

For the patients where a procedure was finally not started (i.e. echo results) or started but finally interrupted with no use of the study device, the discharge date will be registered as the study termination date and no more data will be collected for these patients.

For the patients where a procedure attempt has been made, Harpoon device used, but procedure was finally not completed and patients were converted to another treatment a safety period of 30 days post procedure will be required. Clinical data will be collected and CRF completed until that date. The 30 days Follow up date will be registered as the study termination date for these patients.

For the patients successfully treated, the expected follow period is 24 months. Patients will be followed until that date except under certain circumstances (withdrawal, death, lost to follow up).

Prior to dismissal all patients shall undergo a comprehensive pre-dismissal TTE, as well as a physical assessment (vide supra) in accordance with the schedule of Clinical Investigations.

Patient follow-up: The expected follow up period after the Harpoon procedure is from 24 months. Assessments will be completed at 30days, Discharge, 6 months, 12 months and 24 months.

30 days follow up (+10/0 days post procedure) - Patients will be seen in the outpatient clinic and the following exams will be performed:

- Physical exam, including NHYA evaluation if needed
- ECG
- TTE AE evaluation
- Concomitant medication changes

6 months follow up (+/- 30 days) - Patients will be seen in the outpatient clinic and the following exams will be performed:

- Physical exam, including NHYA evaluation if needed
- TTE
- AE evaluation
- Concomitant medication changes

12 months follow up (+/- 30 days) - Patients will be seen in the outpatient clinic and the following exams will be performed:

- Physical exam, including NHYA evaluation if needed
- 6 minute walk test (6MWT)
- SF36 questionnaire
- TTE
- AE evaluation
- Concomitant medication changes

24 months follow up (+/- 30 days) - Patients will be seen in the outpatient clinic and the following exams will be performed:

- Physical exam, including NHYA evaluation if needed
- TTE
- AE evaluation
- Concomitant medication changes

The table below summarizes the general and cardiac assessments and expected follow up.

General Assessment	PL study site Responsibility	Harpoon Medical Responsibility	Screening and pre-operative evaluation	Surgery Date	Discharge	30 Days (+ 10/-0 d)	6 Months (+/- 30 d)	12 Months (+/- 30 d)	24 Months (+/- 30 d)
Invitation to enroll in the study	X		X						
Screening worksheet completed	X		X						
Patient Eligibility Committee Assessment		X	X						
Patient Information Sheet Signed	X		X						
Pre-Procedure worksheet completed	X		X						
Release of Medical Information **	X		X						
Medical History **	X		X			X	X	X	X
Medications & Dosage **	X		X	X	X	X	X	X	X
Physical Exam **	X		X		X	X	X	X	X
Laboratory Assessment (blood work)	X		X						

** - included as part of the baseline/pre-procedure worksheet

Cardiac Assessment	PL study site Responsibility	Harpoon Medical Responsibility	Screening and pre-operative evaluation	Surgery Date	Discharge	30 Days (+ 10/-0 d)	6 Months (+/- 30 d)	12 Months (+/- 30 d)	24 Months (+/- 30 d)
Chest Radiograph (X-Ray)	X		X						
Diagnostic Left Heart Catheterization or Clinical Standard of Care	X		X						
NYHA Heart Failure Class	X		X			X	X	X	X
Electrocardiogram (ECG)	X		X			X			
Transthoracic Echocardiogram (TTE) ***	X		X		X	X	X	X	X
Transesophageal Echocardiogram (TEE)	X		X	X					
SF-36 Quality of Life Assessment	X		X					X	
6 Minute Walk Test	X		X					X	
EUROscore risk assessment	X		X						
Pulmonary Function Test (if clinically indicated)	X		X						

*** TEE: may be required if the TTE images are not readable

UNSCHEDULED FOLLOW UP VISITS

If the patient is seen by the investigator or center outside planned study follow-up, an unscheduled follow-up visits eCRF should be completed. In the case of adverse event occurrence the corresponding eCRF, documentation, and notification should be completed. In the case of a serious adverse event the corresponding eCRF and documentation should be complete in addition to notifying the Sponsor/Monitor in case the SAE is the cause of the unscheduled visit.

PATIENT WITHDRAWAL FROM THE STUDY

A withdrawal refers to a patient who is determined to be inactive in the study due to physician discretion, patient or family choice (if the patient becomes incapacitated and is unable to continue with the study due to a family choice), and loss to follow-up or patient death. Final status shall be reported on all patients as per the informed consent. Three documented phone calls and a registered/certified letter shall be used to assure that there is minimal loss to follow-up.

In the event that patients are not reachable after repeated contact attempts, investigators must quickly clarify their whereabouts and health status with the family doctor or the contact person stated in the patient consent form (e.g., family doctor) as per the applicable regulation in each country. Patients will agree in the data exchange in the informed consent form.

If these efforts to contact the patient and his family doctor/contact person are unsuccessful, the patient shall be considered lost to follow-up. Attempts made to contact the patients and host family doctor/contact person must be recorded by the study center and monitored by the monitor.

END OF PARTICIPATION

Subjects who have finished the required follow-up visits will be considered to have completed the study.

Withdrawal: all patients have the right to withdraw themselves from participation at any point during the study. In addition, PIs also have the authorization to terminate a patient's participation in the study. A description of the reason for the patient's termination will be documented. Reasons for termination include: completion of study, patient's voluntary withdrawal, physician-directed patient withdrawal, and death.

Upon study exit the patient will be followed per standard of care by the investigator and/or another physician.

DURATION OF INVESTIGATION

The estimated duration for the main investigational plan (e.g. from start of screening to last participant processed and finishing the study) is approximately 36 months.

Each patient will be followed for 24 months and then exit the investigation. It is anticipated that all clinical investigation patients will be enrolled within a 24 month time period.

VIII. SAFETY MANAGEMENT

Subjects will be carefully monitored during the study for possible Adverse Events (AEs) from the time the Subject signs the Patient Informed Consent form to the completion of their participation in the study. Any AE observed will be fully investigated by the Investigator and classified in line with the definitions of the ISO14155:2011 below.
DEFINITIONS

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

This definition includes events related to the investigational medical device.
This definition includes events related to the procedures involved.
For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE):
Adverse event that:
a) led to death,
b) led to a serious deterioration in the health of the patient, that either resulted in
a life-threatening illness or injury, or
a permanent impairment of a body structure or a body function, or
in-patient hospitalization or prolongation of existing hospitalization, or
in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, 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.

Adverse Device Effect (ADE):
Adverse event related to the use of an investigational medical device

NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2: This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse 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.

Anticipated Serious Adverse Device Effect (ASADE)

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.

EVENT SEVERITY

Event severity is classified as follows:

- **Mild:** awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
- **Moderate:** interferes with the patient's usual activity and/or requires symptomatic treatment
- **Severe:** symptom(s) causing severe discomfort and significant impact on the patient's usual activity and requires treatment.

CAUSALITY RELATIONSHIP

The investigator will assess the causality of all adverse events in relation to the research, i.e., the relationship between the AE / SAE and the investigational treatment or any other study-related procedures.

Each SAE will be classified according to five different levels of causality:

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 patient 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 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 patient 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.

INVESTIGATOR REPORTING RESPONSIBILITIES

Notification of events to the sponsor

The investigator should report to the sponsor the following events, whether expected or not, in the corresponding sheet of the eCRF, with the exception of AEs / SAEs detected before the patients has signed the patient consent form.

- AE
- SAE
- Device Deficiencies that did not but might have led to a SAE if:
  i. Suitable action had not been taken or
  ii. Intervention had not been made or
  iii. If circumstances had been less fortunate
- New findings/updated in relation to already reported events

If an AE / SAE is present at the beginning of study prior to the patient providing signed consent to participate in the study, only its worsening should be reported.

The investigator shall notify the sponsor immediately and not later than 24 hours after the investigator has become aware of a SAE or device deficiency that might have led to a SAE. The investigator must ensure that all additional relevant information that becomes available is also forwarded to the sponsor immediately after the initial notification.

The investigator shall transmit to the sponsor all relevant supporting documents related to the SAE (i.e., copy of laboratory exams, hospitalization reports indicating the SAE) ensuring anonymization of the documents and indicating the identification number of the patient in the study.

How to report

The investigator will report "to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports" [ISO 14155:2011 § 9.8 b]. Device malfunctions and use errors should also be reported without unjustified delay.

All Serious Adverse Events (SA(D)Es), including all device deficiencies should be reported to the Sponsor within 24 hours of awareness of an event via the Adverse Event electronic Case Report Form in the study's electronic database, as that will trigger an immediate e-notification to the Sponsor and MedPass. Additional information can be provided to the Sponsor or MedPass via email, telephone, or fax using the information below.

Sponsor:

Harpoon Medical Inc.
351 West Camden Street
Suite 801
Baltimore, MD 21201, U.S.A.
+1 410-346-5687
rvillanueva@harpoonmedical.com

Monitor:

MedPass International
95 Bis Boulevard Pereire
75017 Paris, France
Tel. +33 1 42 12 83 30
Fax: +33 1 40 53 81 11
fredericbillaut@medpass.org

The investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, severity, relationship to the investigational device and/or procedure, required interventions, duration, and outcome. The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the patient is lost to follow-up. The investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome or causality.

REPORTING TO EC/CA

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 Committee according to the relevant local regulatory requirements.

The sponsor will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/4 and/or MEDDEV 2.12-1, as applicable.

IX. INVESTIGATIONAL DEVICEDISTRIBUTION AND ACCOUNTABILITY

The PI is responsible for ensuring that the investigational devices are used only under the PI's supervision and are only used according to this protocol and any approved amendments. At the time of each study, Harpoon will provide the proper quantity of investigational devices the persons authorized to participate in the study. Harpoon will maintain adequate records of the receipt and disposition of all investigational devices. Harpoon and/or MedPass shall document in CRFs the lot numbers of the devices used during a case. Unused devices will be taken back by Harpoon Medical upon completion of a patient. No devices will be left at the study site.

X. STATISTICAL ANALYSIS

This is an early feasibility study. The sample size for this study was determined from the first early feasibility study for this device for the treatment of mitral regurgitation at the conclusion of the procedure and at the time of the hospital dismissal and at one year. Specifically the percentage of patients that demonstrate MR reduction from severe to </+ moderate at the conclusion of the procedure and at 30 days. These data will be used to assess the safety and performance of the device when used on a human patient. These data will be used to assess initial safety and performance of the Harpoon Medical Device, and are not designed to test a statistical hypothesis, therefore a formal sample size has not been calculated. All data will be captured on an intent-to-treat basis. Data will be reported as descriptive statistics.

XI. STUDY ORGANISATION

INVESTIGATIONAL SITE PERSONNEL

Investigator and co-investigators

The Investigator is responsible for ensuring that this study is conducted according to this protocol and that signed Informed Consent is obtained from each patient prior to their inclusion in this study.

It is the Investigator's responsibility to ensure that all staff assisting with this study have the appropriate qualifications and are fully instructed on the study procedures and respect patient confidentiality, as specified in the Investigator Agreement with the Sponsor.

The Investigator is responsible for ensuring that the conduct of the study conforms to the EC and Competent Authority (CA) requirements and provides all necessary communication with the EC, but not limited to, annual study reports and required adverse event notifications.
Specific responsibilities:

- An Investigator shall conduct an investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the ISO14155:2011, the signed Investigator Agreement with the Sponsor, the Protocol, applicable national regulations, and any conditions of approval imposed by a local regulatory body, Ethical Committee (EC), or Competent Authority.
- The standardized Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data from the study. The Investigator is responsible for collecting and accurately recording the data generated for this study.
- Investigators will maintain a screening log that will record the date of informed consent, the date of screening, the enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.
- A participating Investigator shall maintain accurate, complete, and current records (listed in detail in the Investigator Agreement) relating to the Investigator's participation in the study for a period of 10 years or longer, as may be required by applicable laws, rules and regulations.
- An Investigator shall prepare and submit complete, accurate, and timely reports on adverse events, withdrawal of EC approval, progress, deviations from the protocol, informed consent,

termination or completion of the study, and other study-related aspects requested by the EC. (These are described in more detail in the Investigator Agreement.)

Study Coordinator

Each site in this study is required to identify a Study Coordinator who will be responsible for, but not limited to, the following:

- Scheduling diagnostic and assessment procedures.
- Informing all study team members of scheduled treatments.
- Paging study team members on the morning of scheduled treatments to ensure that all necessary personnel will be present.
- Entering all study data into the Case Report Forms.
- Maintaining a list of all patients screened for the study and those who have entered the study and their patient numbers.
- Maintaining the Device Accountability Log.
- Scheduling all follow-up visits within the appropriate follow-up windows and ensuring that all follow-up data is collected in accordance with the protocol.

CLINICAL MONITORING

The clinical study site(s) shall be monitored in accordance with policies at Harpoon Medical, Inc. and those federal regulations that pertain to clinical research; namely ISO14155:2011.

A monitoring plan will be developed prior to the initiation of the investigation which outlines the extent and nature of monitoring appropriate for the clinical investigation, including the frequency of visits, the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation.

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the study. These responsibilities include maintaining regular contact with each Investigational site and conducting on-site monitoring visits at the Investigational site to ensure compliance with this Protocol, to verify that accurate and complete data are being submitted in a timely manner, and to verify that the Investigational site facilities continue to be adequate.

Monitors are responsible for assuring that each Investigator and his/her staff clearly understand and accept their obligations under the clinical investigation through site visits, written communications and phone calls between the Monitor and the PI and staff.

During the course of the investigation, the Monitor shall assure that the PI and his/her staff:

- Understand and agree to the requirements of the protocol;
- Agree to their obligations to conduct the study;
- Accept the obligation to obtain informed consent using the approved Patient Information Sheet;
- Have access to an adequate number of suitable patients to conduct the investigation;

- Have facilities adequate to conduct the clinical investigation; and
- Have sufficient time to fulfill his/her obligations under the study;

During the course of a clinical investigation, the Monitor shall periodically visit the clinical investigation site to assure that:

- Changes to the protocol have been submitted and approved by ethics committees;
- Adverse events (anticipated and unanticipated) are recorded and reported in accordance with the spirit of Good Clinical Practices (GCPs), ISO-14155-2011, Declaration of Helsinki, and as per the Investigator Agreement;
- Accurate, complete, and current records are being maintained;
- Patient confidentiality of records and study participation are being maintained; and
- Accurate, complete and timely reports are being made to Sponsor and to the EC.

Patient information shall remain confidential. Should any new knowledge about the patients' medical condition become known, it will be kept confidential. Any data that may be published in scientific journals will not reveal the identity of the patients. Data retrieved (case report forms, surgery reports, discharge summaries, laboratory and test reports, etc.) from the site will identify patients by their patient number / patient name code only.

CLINCAL EVENTS COMMITTEE

The purpose of the Clinical Events Committee (CEC) will be to review specific information obtained from research patients who are participating in the study. The CEC will have the authority to undertake a critical examination of this information and to draw conclusions regarding pre-specified events that may or may not correspond with the conclusions of the investigator or Harpoon Medical for a specific site. Should a discrepancy arise the CEC's conclusion will serve as the final decision for publication.

The CEC will draw its own conclusions as to whether or not certain clinical events occurred as a result of the patient's study participation. Definitions of clinical endpoints are previously established and are recorded in the Clinical Investigation Plan for use by the committee members. The CEC has the authority to request all available data for a given patient and to use state-of-the-art scientific, technical and clinical information in order to reach its conclusions. These conclusions are required to be drawn independently from those of the treating physician, investigator and Harpoon Medical.

The CEC is composed of 3 physicians: 2 Interventional Cardiologists and a Cardiac Surgeon in clinical practice. These physicians should:

- Not participate in the clinical study
- Have no conflict of interest regarding the device under evaluation
- Be independent from the clinical sites

STUDY ADMINISTRATION

Harpoon Medical, Inc. will make necessary efforts to ensure that this study is conducted in compliance with Good Clinical Practices (GCPs), with the ISO14155:2011 and all applicable regulatory requirements.

The clinical investigation shall not begin until the required approval / favorable opinion from the EC or regulatory authority have been obtained. As appropriate, the Sponsor will submit changes to the protocol to the appropriate regulatory authorities for approval and investigators (to obtain Ethics Committee approval) prior to implementing any changes.

Additional requirements imposed by the EC or regulatory authority shall be followed, as appropriate.

Source Documentation

The Investigator must maintain detailed source documents on all study patients who are enrolled. Source documents include patient medical records, hospital charts, clinic charts, Investigator's patient study files, as well as the results of diagnostic tests (e.g., laboratory tests). These records will be kept in an individual patient binder and stored in a secured and locked location and must be made available to the Monitor during site visits.

Criteria for Terminating a Study

Harpoon Medical, Inc. reserves the right to terminate the study at any time. The reasons for exercising the right would be for valid scientific or administrative reasons related to protection of the safety, rights or welfare of patients. Investigators and associated EC and CA will be notified in writing in the event of termination.

Possible reasons for study termination include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- A decision on the part of Harpoon Medical, Inc. to suspend or discontinue development of the device

Criteria for Suspending/Terminating a Study Center

Possible reasons for suspending/terminating a study center include, but are not limited to:

- Repeated failure to complete case report forms prior to scheduled monitoring visits
- Failure to obtain written Informed Consent
- Failure to report SAEs/UADEs to Harpoon Medical within 24 hours of knowledge

Protocol Deviations

The Investigator is not allowed to deviate from the protocol.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human patients may proceed without prior approval of the sponsor and the Ethics Committee including these under emergency circumstances. Such deviations shall be reported to the Sponsor as soon as possible and no later than 24hours and to the Ethics Committee, if required, or national regulations

Any deviations should be documented on the appropriate Protocol Deviation Case Report Form. If a Clinical Monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of ISO 14155 or other applicable regulations, or any conditions of approval imposed by the reviewing Ethics Committee,

Harpoon Medical, Inc. will immediately either secure compliance or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the investigation.

Protocol deviations will be analyzed by Harpoon Medical, Inc. for the impact to the overall integrity of the study. Disqualification is warranted when an investigator has repeatedly or deliberately violated governing regulations or has repeatedly or deliberately submitted false information in any report. Where protocol deviations occur which do not warrant disqualification from a study, Harpoon Medical, Inc. will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

Any deviations from the protocol must be documented in detail by the Investigator including date and reasons for each deviation and reported to the study monitor as soon as possible.

REGULATORY CONSIDERATIONS: RECORDS RETENTION POLICY

Sponsor

The Sponsor will maintain copies of correspondence, data, shipment of devices, serious adverse device effects and other records related to the clinical study.

Site

The Sponsor and clinical sites will maintain all records pertaining to this study for a period of at least 15 years following the date on which the investigation is terminated or completed as per national requirements, or the date that the records are no longer required for purposes of supporting a regulatory submission.

Ethics Committee (EC) and Competent Authority (CA) Approval

A center my initiate enrollment in this study only after the Sponsor has received written approval from the appropriate Ethics Committee. Amendments to the protocol should be submitted to the Ethics Committee for either notification or approval. Regulatory and local approvals must be obtained prior to enrolment of the first patient. The Sponsor will arrange regulatory and local approvals for the study.

The Sponsor or its Monitor (MedPass International) will require a copy of any EC and CA correspondence, as well as the final approval letter from the EC and CA, where applicable. These communication will be kept in the regulatory communication binder at each participating site.

DATA QUALITY ASSURANCE

Electronic Case Report Forms (eCRF) specific to this study will be used for the collection and recording of data at the Investigational site. Investigators are responsible for the timely completion and submission of these forms to the Clinical Monitor, but in any event submission must be made before payment to the Investigational site is required. All data collected will be entered by MedPass into a database. All case report forms received will be reviewed, tracked and filed. Prior to data entry, a pre-entry review will be conducted to ensure that mandatory fields have been completed. Incoming data will be reviewed to identify inconsistent or missing data and adverse events. Data problems will be addressed through written communication with the investigational site and/or during site visits. The Investigator will be queried on errors concerning data

completeness and consistency. All hard copy forms and data files will be secured to ensure confidentiality.

Investigators are to maintain all source documents, including diagnostic test reports, laboratory results, completed case report forms, supporting medical records and informed consent. The source documents will be referenced during monitoring visits to verify the information documented on the case report forms.

STATEMENT OF INSURANCE POLICY

Harpoon Medical, Inc. shall, at its own expense, carry and maintain professional and general liability insurance or clinical investigation from a carrier in amounts sufficient to cover the covering the cost of treatment of patients in the event of clinical-investigation-related
Injuries, in accordance with the national regulation.

XII. ETHICAL CONSIDERATIONS

DECLARATION OF HELSINKI

This study will be conducted in accordance with the Declaration of Helsinki (see Appendix A).

PATIENT INFORMATION AND INFORMED CONSENT

Patient Information and Informed Consent documents (including the Patient Information sheet) will be submitted to the local site's Ethical Committee for approval prior to initiation of the study. A copy of the consent form approved by the local clinical site's Ethics Committee will be maintained in the official clinical files. All signed consent forms will be reviewed by the Monitor to ensure that only the approved version is being used.

Patients eligible for the study will receive detailed written information on the study, after which they will be asked to give *written* informed consent in accordance with the local clinical site's Ethics Committee. *Oral consent is not an acceptable substitute.* The patient should be asked to sign a consent form prior to undergoing any study-required procedures or assessments. A copy of the Patient Informed Consent document and the Patient Information Sheet will be given to the patient.

The date that consent is obtained must be documented on the consent form and in the patient's medical record.

PATIENT CONFIDENTIALITY

All information concerning patients or their participation in this study will be considered confidential. Only authorized Harpoon Medical personnel and designated consultants and regulatory agencies will have access to these confidential files. Enrolled patients will be assigned a unique identifier that will be used to maintain confidentiality of each patient's medical information. Patient names and other protected health information will not be captured on the case report forms. In addition, angiographic and ultrasonic images submitted from the

participating site to the Sponsor or angiographic reviewers for analysis should be redacted from all patient identifiers.

ETHICS COMMITTEE

A center will initiate enrollment in this study only after the Sponsor has received copies of the written approval of the protocol and Patient Informed Consent from the appropriate Ethics Committee. Any subsequent amendment to the protocol should be submitted to the Ethics Committee for either notification or approval.

REGULATORY APPROVAL

Regulatory and local approvals must be obtained prior to enrollment of the first patient. The Sponsor will arrange regulatory and local approvals for the study.

XIII. QUALIFICATIONS OF STUDY CENTERS AND INVESTIGATORS

Each investigator must fulfill the following requirements prior to participation in this study:

- Be appropriately trained on the use of the Harpoon Medical Device and procedure.
- Be willing to change their clinical / surgical routine if required by the protocol.
- Have an adequate medical Ethics Committee and be willing to comply with Good Clinical Practice, and the European standard ISO14155:2011 for the conduct of clinical investigations of medical devices.
- Be willing to fill out all relevant documentation (e.g. Case Report Form) in a suitable, legible and timely manner, not to exceed 30 days, to allow analysis.
- Be willing to allow clinical monitors to enter at reasonable times for inspection of all records pertaining to the study.

XIV. PUBLICATION POLICY

Sponsor follows local regulatory requirements relating to clinical trial registration and disclosure of results. In the United States, Harpoon Medical Inc. complies with requirements of the FDA Amendments Act of 2007 (FDAAA) to register this study on www.clinicaltrials.gov.

Sponsor commits to seek publication of results of its clinical studies in the peer-reviewed scientific literature, regardless of study outcome. Sponsor supports recognized standards concerning authorship and publication, including those of the ICMJE (International Committee of Medical Journal Editors) and CONSORT (Consolidated Standards of Reporting Trials). In the event that the Sponsor decides not to CE Mark the Investigational Medical Device for the intended purpose being investigated, the Sponsor shall publish the analysis of the results within twenty four (24) months of the completion of this study. In the case of Clinical Investigations closed on safety grounds, the Sponsor shall publish the analysis of the results within twelve (12) months of the date of closure.

The Sponsor and the Investigators are committed to the publication and widespread dissemination of the results of the study. This study represents a joint effort between Sponsor and Investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation. Patient to the terms of Confidentiality but not before

publication of the multi-center study results, Institution and the Investigator shall be free to publish, present or use any results arising out of the performance of the study at their centers for their own instructional, study or publication objectives, provided that such Publication does not disclose any Confidential Information other than the results of the Study performed. At least one hundred and eighty (180) days prior to submission for publication, presentation or use, Institution and the PI shall submit to Sponsor for review and comment any proposed oral or written Publication, which period may be extended for an additional thirty (30) days if requested in writing by Sponsor in the event that Sponsor provides reasonable need for such extension. Expedited reviews for abstracts or poster presentations may be arranged if mutually agreeable to Sponsor, Institution and the PI.

Upon written notice to Institution that Sponsor reasonably believes that one or more patent applications relating to an Invention (as defined above) should be filed prior to any Publication, then such Publication will be delayed until such patent application(s) have been filed, provided that Institution, PI and Sponsor shall cooperate in expeditiously filing any such patent application(s), and provided further that any such delay of a Publication shall not exceed ninety (90) days from the date of such Sponsor notice to Institution and PI. Sponsor shall have the right to request modification of any Publication if in Sponsor's reasonable opinion such Publication will jeopardize a patent application or patent. Harpoon Medical Inc. has the right to review all proposed publications and presentation materials for scientific integrity, effect on clinical activities, and relevance to patent protection and partnership agreements. Harpoon Medical Inc. will not suppress publications or presentations, but reserves the right to delay publications to avoid compromising intellectual property. Additionally, Harpoon Medical Inc. reserves to right to delay publications of sub-analyses until after the publication of the main study results.

Sponsor will provide final reports of protocol-derived outcomes to external authors. Sponsor reserves the right to review and comment on draft abstracts, manuscripts, presentations and other communications by external investigators related to this study or a subset analysis of any patients enrolled in this study, prior to submission or public disclosure, in order to protect intellectual property and confidential information. As study sponsor, Harpoon Medical, Inc. does not approve or veto such publications provided they are made after the publication of the main publication disclosing the multi-center study results.

Authorship and accountability: Per ICMJE recommendations, an author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on 1. Substantial contributions to study conception and design, or acquisition, analysis and interpretation of data, *and* 2. Drafting the article or revising it critically for important intellectual content, *and* 3. Final approval of the version to be published, *and* 4. Agreement to be accountable for all aspects of the work to ensure its accuracy and integrity. *All four conditions should be met.* Conversely, individuals who do not contribute in this manner do not warrant named authorship. Individuals who do not meet criteria for authorship but who contributed materially to the manuscript will be recognized in acknowledgments when the manuscript is published. In some cases, journals recognize contributors rather than authors. Patient to journal policy, we will list the names of all investigators at the end of a manuscript. Final authorship determination will be made the sponsor in accordance with ICMJE recommendations. Determination of meeting (for an abstract presentation) or journal (for a manuscript submission) will be mutually agreeable to Sponsor, Institution and the investigators.

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