



Edwards

CE Mark Study for the Harpoon Medical Device

Mitral TRans-Apical NeoChordal Echo-guided Repair (TRACER)  
Trial

NCT02768870

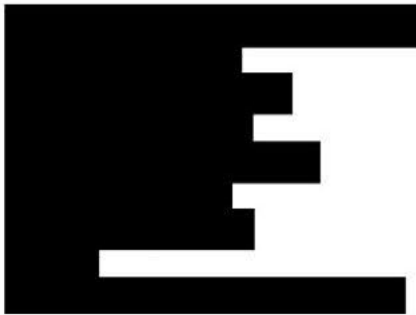
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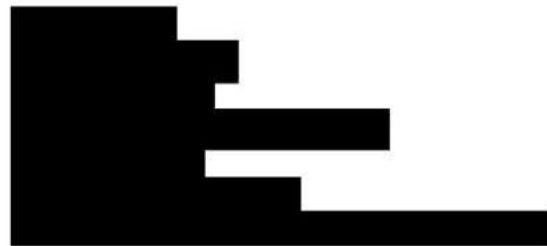
**Monitor:**



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**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. Authorised recipients of this information include investigators and co-investigators, other health care personnel necessary to conduct the study and Institutional Review Boards / 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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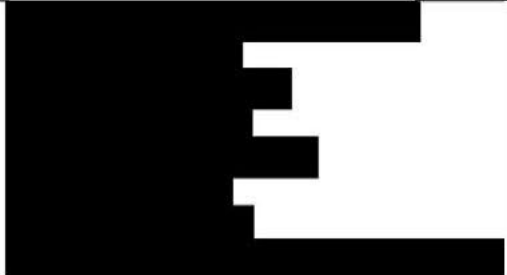


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## ABBREVIATIONS

AE	Adverse event
CA	Competent authority
CE	Conformité Européene
CEC	Clinical events committee
CKD	Chronic kidney disease
CRF	Case report form
EC	Ethical Committee
EFS	Early feasibility study
eCRF	Electronic case report form
ePTFE	Expanded polytetrafluoroethylene
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
GCP	Good clinical practices
GFR	Glomerular filtration rate
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	Identity Number
IDMJE	International Committee of Medical Journal Editors
MDD	Medical Device Directive
MR	Mitral Regurgitation
NYHA	New York Heart Association
PA	Pulmonary Artery
SAE	Serious Adverse Event
SOC	Standard of Care
TOE	Transoesophageal Echocardiogram
TTE	Transthoracic Echocardiogram
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organisation

**I. PRIMARY CONTACTS**

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<b>Principal Investigator(s)</b>		<p><i>Please refer to Annex I for the list of all principal Investigators and coordinating centers</i></p> <p><i>Protocol Signature pages are provided separate to this protocol</i></p>

## II. STUDY SUMMARY

<b>Title:</b>	Mitral <b>T</b> Rans- <b>A</b> pical Neo <b>C</b> hordal <b>E</b> cho-guided <b>R</b> epair (TRACER) Trial
<b>Protocol Number:</b>	HMCE -1002-00k
<b>Study Status:</b>	Enrollment was completed as of November 2017. Follow-ups range from 6 to 36 months. The purpose of this amendment is to extend to 5 years of follow-up post-implant.
<b>Design:</b>	This is a prospective, single arm, nonrandomised, multi-center EU study to demonstrate the performance and safety of the Harpoon Medical device in patients with degenerative MR.
<b>Study Duration:</b>	Projected enrollment of first patient: April 2016 Projected exit of final patient: November 2022
<b>Primary Objective:</b>	The primary objective of this study is to evaluate the safety and performance of the Harpoon Medical device.
<b>Patient Population:</b>	Patients with “Severe” mitral regurgitation as a result of posterior leaflet prolapse.
<b>Sample Size:</b>	Up to twenty (20) patients in the UK will be enrolled.
<b>Number of Sites:</b>	Up to eight (8) sites in up to four (4) countries. Each country will enroll up to twenty (20) patients.
<b>Treatments:</b>	Up to eight (8) pairs of ePTFE chordae tendineae may be placed in the posterior leaflet of the mitral valve using the Harpoon Medical Transapical Device in order to establish effective coaptation of the mitral leaflets.
<b>Endpoints:</b>	<b>Performance endpoints:</b>  <b>Primary Performance Endpoints:</b> To demonstrate that the Harpoon Medical device performs as designed and has the ability to successfully implant one or more ePTFE chordae tendineae on 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.  <b>Secondary Performance Endpoints:</b> Severity of mitral regurgitation at 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months follow-up shall be tracked and recorded.

### **Safety Goals:**

**Primary Safety Endpoints:** Procedure freedom from Serious Adverse Events (SAEs) during the ePTFE implantation procedure, at discharge, and at 30 days follow-up shall be tracked and recorded.

**Secondary Safety Endpoints** Freedom from Serious Adverse Events (SAEs) at 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months follow-up shall be tracked and recorded.

### **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
- 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
- Anterior or bileaflet prolapse
- Functional MR
- 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 Transoesophageal echocardiography
- Severe left or right ventricular dysfunction
- NYHA Class IV
- Renal insufficiency CKD stage 3b or worse (GFR < 45 ml/min/1.73 m<sup>2</sup>)
- 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, 18 months 24 months, 30 months, 36 months, 48 months and 60 months after implantation.



### III. INTRODUCTION

#### **Mitral Regurgitation, Transapical mitral valve repair, and the Harpoon Medical device**

Mitral valve disease is the second common valvular heart disorder requiring surgery in Europe, with nearly 8 million Europeans estimated to have severe mitral valve regurgitation (“MR”). MR results in a volume overload on the left ventricle which in turn leads to ventricular dilation, decreased ejection performance, pulmonary hypertension, symptomatic congestive heart failure, atrial fibrillation, right ventricular dysfunction and death. Successful surgical mitral valve repair restores mitral valve function, abolishes the 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 functional ischemic or idiopathic MR (the motion of the normal mitral valve leaflets is restricted by the enlarged ventricle) both of which lead to ineffective valve closure and regurgitation.

Two-thirds of all Mitral valve procedures in North America are performed on patients with degenerative MR and that percentage is estimated to be similar in the European Union (EU). Open cardiac surgery is a common method of treating degenerative mitral valve regurgitation which involves replacing and/or supplementing elongated or ruptured chords with artificial chords made of ePTFE, a commercially available material which has a 20+ year history of safety in conventional mitral valve repair procedures. While open cardiac surgery has a low mortality risk (less than 1%) and is evidenced to have excellent long term outcomes, it has risks, including stroke, bleeding, infection, and the risk of valve replacement rather than repair. It is anticipated that use of the Harpoon device could achieve similar outcomes while decreasing the invasiveness of mitral valve repair.

#### DEVICE DESCRIPTION

The Harpoon Medical Transapical device is intended to be used 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. Harpoon Medical has developed a novel small-diameter (< 3 mm) rigid linear delivery system using a needle wrapped with ePTFE in a pre-formed knot configuration. The device delivers replacement chordae using a valved introducer inserted a few centimeters “off apex” using Transoesophageal echocardiography (TOE). To deploy the pre-formed knot on the atrial side, the delivery system is actuated to advance the needle and pre-formed knot through the leaflet. The delivery system then retracts the needle, leaving the pre-formed knot on the atrial side of the leaflet. After deployment, the delivery system is withdrawn from the valved introducer, exposing the replacement chordae tendineae. The procedure may be repeated up to 4 times using a single valved introducer. The replacement chordae tendineae are adjusted under real-time TOE to optimise the surface of coaptation between leaflets before they are secured to an ePTFE pledget on the epicardium.

#### 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 TOE-guided chordal 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 20+ 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.

Conventional mitral valve surgical procedures require a 3 to 6 hour operation with about 7 days (including at least 1 to 3 days in the Intensive Care Unit (ICU))<sup>1</sup>. Recovery after valve surgery may take a long time, depending on how healthy the patient was before the operation. Patients with an office job, can usually go back to work in 4 to 6 weeks. Those who have more physically demanding jobs may need a longer recovery period. It is anticipated that the Harpoon procedure time will be reduced to 1 to 2 hours (average procedure time of 110 minutes) and recovery times would be substantially shorter due to the less invasive nature of the procedure. Collectively, the benefits of the Harpoon procedure should translate into less pain and disability, shorter hospital lengths of stay, fewer strokes, less renal failure, fewer wound infections and lower peri-procedural mortality.

There are alternate treatments available to replace ruptured or elongated chordae tendineae and reduce MR. However, there is no currently effective medical therapy that treats or cures MR, and the alternate procedures to repair the mitral valve are generally more invasive, 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 either require a sternotomy or a thoracotomy, cardiopulmonary bypass, aortic manipulation and cardioplegic cardiac arrest. Mitral valve repair is carried out with leaflet resectional techniques (Carpentier) or nonresectional techniques using ePTFE chordae tendineae placed under direct vision. Because the heart is flaccid and arrested, sizing the chordae tendineae is difficult. Improper sizing of the chordae tendineae may result in a failed or ineffective mitral valve repair. The success of mitral valve repair is significantly dependent on the expertise of the operating surgeon. For patients with degenerative mitral valve disease, mitral valve replacement is inferior to mitral valve repair (short-term higher perioperative mortality and long term substantially higher risks of stroke and prosthetic valve endocarditis as well as either the need for lifelong anticoagulation (mechanical valve) or the risk of repeat mitral operation (bioprosthetic valve). Mitral valve replacement (compared to repair) is a risk of open cardiac surgery. This procedure is also very invasive and not a feasible option for all patients.
- In 2008, Evalve received a CE mark for the MitraClip in the EU. Shortly thereafter, the company was acquired by Abbott Labs. The implantation of MitraClip does not involve open-heart surgery, but mimics the surgical method of edge-to-edge valve repair where the mitral valve leaflets are clipped together with the device instead of being sutured together. Extensive clinical experience with the MitraClip has been collected over the last six years and the clinical efficacy has been mixed.

<sup>1</sup> <http://www.rbh-specialistcare.co.uk/diagnosis-treatments/heart-treatments/valve-repair-or-replacement-incl-tavi-mitral-valve-repair/>

- In 2013, NeoChord released a CE marked, Class III medical device to the EU as a minimally invasive procedure that is performed on a beating heart to replace chordae tendineae that have become elongated or ruptured. NeoChord does not involve open-heart surgery, but mimics the surgical method of suturing the free-edge of the mitral valve to install replacement chordae tendineae. Initial clinical results have been promising, but the device requires the surgeon to enter the left ventricle with a large shaft (~3x larger than the Harpoon device) for every suture. Suture placement is limited to the free edge of the mitral leaflet and requires the operator to grasp a moving mitral leaflet for deployment.

Although these procedures are available to cardiothoracic surgeons in the EU, there is still a need for additional minimally invasive treatment options for patients suffering from MR. Based on the outcomes from the EFS, it is expected that the Harpoon Medical device will be a valuable treatment alternative for patients suffering from MR.

## POTENTIAL RISKS

There are risks associated with our protocol. The Harpoon Medical device received CE Mark in December 2017. The study uses minimally invasive surgical techniques to repair/replace the native chordae in a human heart. The discomforts and risks that we predict 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., localised pain, discomfort at the incision site(s) and the risks of bleeding, injury to the myocardium and injury to the mitral valve). If the Harpoon Medical device does not perform as designed, classical definitive repair of the mitral valve using conventional open-heart procedures and cardiac bypass will be used to facilitate the repair. There may be a possibility that the TRACER procedure causes the classical definitive repair that would be carried out subsequently, if needed making the classic repair more technically and clinically difficult.

#### IV. STUDY OBJECTIVES

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

##### PERFORMANCE GOALS

**Primary Performance Endpoints:** To demonstrate that the Harpoon Medical device performs as designed and has the ability to successfully implant one or more ePTFE chordae tendineae on 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, 18 months, 24 months, 30 months, and 36 months follow-up shall be tracked and recorded.

##### SAFETY GOALS

**Primary Safety Endpoints:** Procedure freedom from Serious Adverse Events (SAEs) during the ePTFE implantation procedure, at discharge, and at 30 days follow-up shall be tracked and recorded.

**Secondary Safety Endpoints** Freedom from Serious Adverse Events (SAEs) at 6 months, 12 months, 18 months, 24 months, 30 months and, 36 months follow-up shall be tracked and recorded.

## V. STUDY DESIGN

This is a prospective, single arm, nonrandomised, multi-center EU study to demonstrate the performance and safety of the Harpoon Medical device in patients with degenerative MR.

## VI. STUDY POPULATION

### NUMBER OF PATIENTS

Up to 20 patients in the UK may be enrolled. The estimated enrollment period is 24 months, and all patients shall be followed for 30 days, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months and 60 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 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
- 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
- Anterior or bileaflet prolapse
- Functional MR
- 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 Transoesophageal echocardiography
  - Severe left or right ventricular dysfunction
  - NYHA Class IV
  - Renal insufficiency CKD stage 3b or worse (GFR < 45 ml/min/1.73 m<sup>2</sup>)
  - 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

#### 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. If these efforts to contact the patient are unsuccessful, the patient shall be considered lost to follow-up.

## VII. PATIENT ENROLLMENT

### INFORMED CONSENT

Patients who are screened and for whom the principal investigator feels would be a good candidate for inclusion in the Mitral TRACER 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. Study personnel should explain that even if a patient agrees to participate in the study and signs the Patient Information Sheet, the patient may not be eligible to participate if he/she fails additional eligibility criteria.

A Screening/Enrollment Log will be maintained in the on-site clinical records located at the study site to document select information about candidates who fail to meet the entry criteria.

### ENROLLMENT

Patients will be considered enrolled in the Mitral TRACER Trial once informed consent has been signed and all eligibility criteria confirmed, including intra-operative assessment of suitability of the patient's mitral valve for Harpoon device treatment.

### SCREENING/ PRE-PROCEDURE

**Screening evaluations:** All patients that are identified as potential candidates for the study shall undergo transthoracic echocardiography (TTE) OR TOE. A TOE will be performed at the referring doctor's request or if the Harpoon Medical determines that the TTE images are not readable. Both the TTE and TOE are routine preoperative studies for patients undergoing heart valve surgery.

The screening evaluations will be sent to the Harpoon Medical Patient Eligibility Committee (PEC) who will independently assess the eligibility of the patient for participation in the TRACER study. 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, the patient 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.

**Pre-procedure/baseline evaluations:** Once the patient is enrolled for the Harpoon Medical procedure, a Physical Assessment will be performed. This includes a comprehensive history and physical examination, including the listing of all medications and dosage. Additionally, the following physical assessments shall be completed:

- 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 catheterisation (LHC) may be required for all patients  $\geq$  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

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 heparinised saline to achieve an activated clotting time of  $\geq 350$  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 TOE 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 singled valved introducer, to secure and align apposition between the anterior and posterior mitral leaflets. If more than four (4) suture pairs are required, the valved introducer 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 as 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 TRACER procedure or at a later date/time at the discretion of the operating surgeon. Subjects who undergo a conversion to SOC mitral valve surgery via a median sternotomy will be followed up for 30 days.

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



**Patient follow-up:** Patients shall be seen in the outpatient clinic 30 days (+10 days/-0 days) after the Harpoon procedure. A TTE and a clinical assessment shall be performed at that time (in accordance with the schedule of Clinical Investigations) to evaluate the device against the primary and secondary performance and safety endpoints.

Additional clinical and TTE follow-up in a registry fashion shall occur for all active subjects (in accordance with the Clinical Investigations defined in the table below) at the following intervals:

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

If due to an increase of MR, or due to any other medical circumstances, and a study patient has to undergo a Mitral Valve reoperation, this patient will be followed up by the study team for 30 days and then will be exited from the study

## VIII. CLINICAL INVESTIGATIONS

General Assessment	UK 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)	18 Months (+/- 30 d)	24 Months (+/- 30 d)	30 Months (+/- 30 d)	36 Months (+/- 30 d)	48 Months (+/- 30 d)	60 Months (+/- 30 d)
Invitation to enroll in the TRACER 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	X	X	X	X	X
Medications & Dosage **	X		X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam **	X		X		X	X	X	X	X	X	X	X	X	X
Laboratory Assessment (blood work)	X		X											

\* An additional Patient Information Sheet will be signed by the subject(s) to reflect the additional follow-up required by this protocol amendment

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

Cardiac Assessment	UK 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)	18 Months (+/- 30 d)	24 Months (+/- 30 d)	30 Months (+/- 30 d)	36 Months (+/- 30 d)	48 Months (+/- 30 d)	60 Months (+/- 30 d)
Chest Radiograph (X-Ray)	X													
Diagnostic Left Heart Catheterisation or Clinical Standard of Care	X		X											
NYHA Heart Failure Class	X		X			X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X		X			X								

Transthoracic Echocardiogram (TTE) ***	X		X		X	X	X	X	X	X	X	X	X	X
Transoesophageal Echocardiogram (TOE)	X		X	X										
SF-36 Quality of Life Assessment	X							X						
6 Minute Walk Test	X							X						
EUROscore risk assessment	X													
Pulmonary Function Test (if clinically indicated)	X													

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

## RETROSPECTIVE COLLECTION OF DATA

Protocol Version 00k extends the patient follow-up with visits at 48 and 60 months. The Protocol Version 00j had introduced additional follow-up visits at 18, 30 and 36 months. These protocols allow retrospective collection of data on any scheduled or unscheduled visit that the subjects participated in for the TRACER trial (if subject came back to the hospitals) before Versions 00j or 00k are approved by Ethic Committee (EC) and Competent Authority (CA).

Once Protocol Version 00k has been approved by relevant EC and CA, patients will be contacted and asked to consent to the additional visits and have their data collected. Patients who exited from the trial at 36 months as scheduled per protocol Version 00j will be contacted and requested to continue their follow-up up to 60 months as scheduled by Protocol Version 00k.

Two different versions of information letters will be sent depending on patient status (already exited or not). Each patient will have to sign this letter to approve collection of additional data.

## SEVERITY AND CAUSALITY ASSESSMENT

The occurrence of Adverse Events (AE's) will be monitored during this study. All AE's will be recorded on the Adverse Event Form at onset and at each follow-up visit until resolved. To meet the objectives of this study, the following definitions will apply. (Definitions reference ISO 14155:2012-01 and MEDDEV 2.7/3, December 2010)

**Adverse Event (AE):** Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device. This includes events related to the device or events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons, this definition is restricted to events related to investigational medical devices.

**Adverse Device Effect:** An adverse event related to the use of an investigational medical device, including adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation or operation, or any malfunction of the medical device or any event resulting from use error or intentional misuse of the medical device.

All AEs will be monitored from the time of the Harpoon Medical procedure through the 60 month follow-up visit. All AEs observed by the Investigator or staff during a physical or laboratory examination, interventional procedure, or mentioned by the patient either spontaneously or upon questioning will be recorded on the AE case report form. Information pertaining to all AEs will be reviewed and verified by the study Sponsor's Safety Team or its designated representative. The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The following categories of adverse event severity are to be used:

- 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 clinical sequela.
- Moderate: Interferes with the patient's usual activity
- Serious: Any fatal or immediately life-threatening clinical experience that requires a patient to be hospitalised, or hospitalisation is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes any permanently disabling event.

**Device deficiency:** Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as a malfunction, misuse or use error and inadequate labeling.

**Investigational medical device:** A medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

**Serious Adverse Device Effect (SADE):** An adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

**Serious Adverse Event (SAE):** A serious adverse event is any problem encountered in a licensable clinical trial that has led to death or to a serious deterioration in the health of a 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 hospitalisation or prolongation; or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. This includes device deficiencies that might have led to a serious adverse event if suitable action had not been taken or if intervention had not been made or if circumstances had been less fortunate.

Note: Planned hospitalisation for a pre-existing condition, or a procedure un-related to the mitral valve treatment or a procedure required by this study, that is without serious deterioration in health, is not considered a serious adverse event.

SAEs must be reported via eCRF (electronic case report form) immediately but no later than 3 calendar days upon site awareness.

All SAEs and device deficiencies (reported by Investigators or identified by Safety) will be adjudicated by an independent Clinical Endpoint Committee (CEC) through the 36 month follow-up, based on relevant source documents provided from the investigational sites.

The CEC will verify SAE criteria and code. For all confirmed SAEs, CEC will also conduct a causality assessment in regards to the investigational Harpoon device and the index procedure. All adjudication activities are managed by Sponsor's Safety team according to the CEC Charter.

**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.

UADEs must be reported to MedPass Limited by telephone and/or email within 24 hours upon site awareness.

## REPORTING ADVERSE EVENTS, DEVICE MALFUNCTIONS AND FAILURES

All SAEs and Investigational Medical Device deficiencies that might have led to a SAE if suitable action had not been taken or if intervention had not been made or if circumstances had been less fortunate or if any new findings/updates in relation to already reported event have been made. These events shall be recorded on the Adverse Event CRF by the Investigator (or his/her designee) immediately but no later than 3 calendar days upon site awareness. The report should include: identification of the event, country, study center, patient ID code, date of procedure/first use, date of event onset, description of the event, action/treatment/patient outcome, assessment of relationship to the procedure (yes, no, possibly), assessment of relationship to the investigational device (yes, no, possibly), unanticipated SADE (yes/no), event status (resolved, resolved with sequela, ongoing, death), and the date of the event resolution.

In the case of serious adverse events (SAE), procedure and/or device failures and malfunctions, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to Harpoon Medical or its designee, if requested. If appropriate, the event shall subsequently be reported to the relevant Ethics Committee, and the Sponsor shall inform the Competent Authority within the appropriate timelines.

## DOCUMENTATION, EVALUATION AND NOTIFICATION OF SAEs

All incidents will be captured as a part of this clinical study. At each contact with the patient, the investigator must seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects should be recorded immediately in the source document, and also in the appropriate adverse effect case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document.

In conformity with MDD Directive 93/42/EEC (Article 10), any incident resulting from a malfunction or deterioration in the characteristics and/or performance of the device or inadequacies in the

labeling that might lead or might have led to the death of a patient or user or to a serious deterioration in the state of health of the patient or user or any device deficiency that leads to a systematic recall will be reported to the appropriate authorities. During site visits, the Monitor will follow-up with the Investigator(s) to ensure they have transmitted the information to the appropriate authorities and that the appropriate documentation is retained onsite in the study regulatory binder.

The Investigator shall report all serious adverse events (anticipated or unanticipated) to the Sponsor's UK Legal Representative within 24 hours upon becoming aware of events.

All adverse device effects occurring during the study period must be recorded using the Adverse Event Source Documents and Case Report Forms provided by the Sponsor for documenting adverse events. The clinical course of each event should be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period should be recorded and reported promptly to the appropriate authorities. A follow-up written report, documented on the Adverse Event CRF and including any related clinical documentation, shall be provided as soon as possible and shall include the following information, as applicable:

1. Patient Study ID
2. Event description
3. Statement as to whether it is considered anticipated or unanticipated
4. Statement as to the degree to which it is considered device-related, and why
5. Results of any diagnostic tests that were performed
6. Description of any medical intervention required
7. Status following the intervention
8. Investigator's signature and date on the AE CRF

The Investigator will continue to clinically monitor the adverse event per standard of care until it is resolved, stabilised, or the patient's status returns to pre-event status, documenting the status on appropriate CRFs, including any sequela.

The Sponsor will ensure compliance with all country-specific reporting requirements to the appropriate Ethical Committee and Competent Authority.

## **IX. INVESTIGATIONAL DEVICE DISTRIBUTION AND ACCOUNTABILITY**

### **DEVICE ACCOUNTABILITY**

The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the study. The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The Investigator shall document in CRFs the lot numbers of the devices used during a case. In addition, the Investigator shall keep complete and accurate records of all devices used or unused in a Device Accountability Log, provided by the Sponsor, that have been returned to Harpoon Medical.

### **RETURN OF DEVICES**

All unused investigational devices will be returned to the study Sponsor upon completion of the clinical study. All used investigational devices will be properly disposed of, per institutional procedures. Any investigational device that fails to perform correctly will be immediately returned to the study Sponsor for analysis. The Investigator or his/her designated representative is responsible for device accountability and disposition of all used and unused devices. The study Sponsor or its designated representative will conduct device reconciliation at the completion of patient enrollment or at the conclusion of the study.

## X. STATISTICAL ANALYSIS

Based on the sample size calculations below, a total of 30 patients should be sufficient to demonstrate statistical non-inferiority of the Harpoon Medical device to other devices currently on the market in the EU for less-invasive mitral valve repair in the beating heart with a 90% power using a two-sided  $\alpha$  of 0.05 (one-sided 0.025). The clinical investigation of the Harpoon Medical device involves a multi-center study conducted across multiple countries and up to a total of 20 patients will be enrolled in the UK. Data collected from the first 30 patients enrolled across all sites will be used to support the CE mark of the Harpoon Medical device. Therefore, data from some or all of the 20 patients enrolled in the UK, depending on the timing of enrollment, will be used to support the CE mark of the Harpoon Medical device. The estimated enrollment period for the study is up to 24 months, and all patients shall be followed for 30 days, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months and 60 months after implantation in accordance with the Clinical Investigations schedule provided in Section VIII.

Currently, there are two (2) Class III reference devices on the market in the EU for treating MR due to one or more prolapsed leaflets (degenerative MR): the MitraClip device and the NeoChord DS1000. Both of these devices were designed to reduce MR on a beating heart without the need to arrest the heart or place the patient on cardiopulmonary bypass. The primary and secondary endpoints used to support CE mark for these devices were: freedom from death and MACE, freedom from surgery for mitral valve repair or replacement, and a reduction of MR to grade  $\leq 2$ . The studies performed in support of CE mark for both the NeoChord and MitraClip devices reported 30 day response rates.

For the MitraClip device, data following treatment with the MitraClip implant demonstrated a success rate for mitral regurgitation reduction to  $\leq$  grade 2 in 58% (14/24 patients) at 30 days, and 54% at 6 months (13/24 patients) (Feldman et al., 2005). In a subsequent randomised trial of MitraClip compared to surgical treatment of mitral valve regurgitation, the success rate was 55% at 12 months (100/181 patients) (Feldman, et al., 2011).

For the initial CE Mark Study of the NeoChord DS1000, data from 30 patients at seven (7) study centers at 30 days post-implant was evaluated in support of the CE Mark. In this study, the primary composite outcome was assessed in patients in whom at least one chordae tendineae was placed using the NeoChord DS1000 System. The composite endpoint consisted of the following elements:

- a reduction in mitral regurgitation  $\leq 2+$  at the time of the procedure AND
- MR reduction of  $\leq 2+$  at 30 days AND
- The rate of Major Adverse Events (MAE) defined as a combined endpoint of: death, MI, reoperation for failed surgical repair, non-elective cardiovascular surgery to treat an adverse event, procedural ventilation > 48 hours, procedure-related transfusion of > 2 units blood product, stroke, renal failure, deep wound infection, new onset of permanent AF, and septicemia, through 30 days.

Based on this definition, the response rate was 57% (17/30 patients) (Seeburger et al., 2014). In two subsequent single-center reports, the composite success rate using the NeoChord DS1000 was 85% (11/13 patients) at 6 months post-procedure (Rucinskis, et al., 2014) and 87% (54/62 patients) at 30 days post-procedure (Colli, et al., 2015). Combining these results, irrespective of the time of assessment of the primary endpoint, the average success rate among these studies is 68%, the standard deviation of the response rate is 15%, and the lower limit of one-sided 95% confidence intervals (CI) is approximately 50%.



An inferiority margin of 10% was selected as appropriate because it is a more stringent requirement than the lower bound of the 95% confidence interval of the average response rates in these previous studies. This non-inferiority delta reflects the diversity of the patients treated, the diversity of the causes of MR, the variety of non-beating heart methods available to treat MR, and the range of reported performance using similar techniques.

Using the historical control (HC) rate of 68% and a non-inferiority margin of 10%, the null and alternative hypotheses of the primary performance endpoint can be written as:

$$H_0: \pi_{\text{Harpoon\_performance}} \leq \pi_{\text{HC\_performance}}$$

$$H_A: \pi_{\text{Harpoon\_performance}} > \pi_{\text{HC\_performance}}$$

where,

$$\pi_{\text{HC\_performance}} = 68\% \text{ historical control rate} - 10\% \text{ Delta}$$

$$\pi_{\text{Harpoon\_performance}} = \text{Harpoon Medical system success rate}$$

The hypotheses for the primary performance endpoint can be rewritten as:

$$H_0: \pi_{\text{Harpoon\_performance}} \leq \text{HC \%}$$

$$H_A: \pi_{\text{Harpoon\_performance}} > 58\%$$

To achieve 90% power using a two-sided  $\alpha$  of 0.05 (one-sided 0.025), the sample size was estimated based on a single sample compared to a constant (0.58). Based on this calculation, 26 patients are required to demonstrate non-inferiority. To adjust for patients lost to follow-up, we have decided to enroll up to 30 patients in the TRACER Trial. Moreover, 30 patients has been a sufficient number of patients to provide a satisfactory profile of the adverse events likely to occur with beating heart mitral valve repairs in the aforementioned studies. Last, 30 patients is consistent with the sample size of previous beating heart, mitral valve repair devices. For example, the CE mark trial of the NeoChord DS1000 was conducted in 30 patients.

These data from these 30 patients shall be used to assess the safety and performance of the device when used on a human patient. All data shall be captured on an intent-to-treat basis. Data shall be reported as descriptive statistics.

The percentage of patients with improvements in MR reduction at the conclusion of the procedure, at the time of the hospital dismissal and at 30 days, six months, one, two, three, four and five years will be assessed. Specifically the percentage of patients that demonstrate MR reduction from “severe” to less than or equal to “moderate” at the conclusion of the procedure and at 30 days. While the number of subjects missing the primary endpoint of improvement in MR is anticipated to be small, if any, the following algorithm will be used to impute missing observations:

- Subjects who die prior to evaluation at 30 days or fail the procedure will be considered failures for the primary analysis.
- Patients lost after the procedure for other reasons will have their last observation carried forward (from procedure to 30 days). Should this situation occur, an additional sensitivity analysis, a tipping point analysis, will be conducted whereby each subject missing 30 day follow-up will be counted as a failure in succession, and the number of subjects with

missing data imputed as failures which “tip” the analysis to non-significance will be reported.

Freedom from Serious Adverse Events (SAEs) during the ePTFE implantation procedure, at discharge, and at 30 days follow-up will be tabulated. The number of patients experiencing one or more AEs or SAEs at 30-days post-procedure, the percentage of patients, and the exact 95% confidence limit will be calculated. Patients who die prior to 30 days will be considered failures for this analysis.

Freedom from Serious Adverse Events (SAEs) at 6 months, 12 months, 18 months, 24 months, 30 months and 36 months follow-up shall be tabulated. The number of patients experiencing one or more AEs or SAEs at 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months and 60 months follow-up, the percentage of patients, and the exact 95% confidence limit will be calculated.

These data shall be used to assess the safety and performance of the Harpoon Medical device, and are not designed to test a statistical hypothesis, and therefore a formal sample size has not been calculated. All data shall be captured on an intent-to-treat basis. Data shall be reported as descriptive statistics.

## **XI. STUDY ORGANISATION**

### INVESTIGATIONAL SITE PERSONNEL

#### Investigator and co-investigators

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

It is the Investigator's responsibility to ensure that all staff assisting with this trial have the appropriate qualifications and are fully instructed on the trial 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 trial conforms to the EC and Competent Authority (CA) requirements and provides all necessary communication with the EC and CA including, but not limited to, annual trial reports and required adverse event notifications. Specific responsibilities:

- An Investigator shall conduct an investigation in accordance with the signed Investigator Agreement with the Sponsor, the Protocol, applicable international regulations, and any conditions of approval imposed by a local regulatory body, Ethical Committee (EC), or Competent Authority.
- The standardised Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data from the trial according to the International Conference on Harmonisation (ICH)/WHO Good Clinical Practice (GCP) standards. The Investigator is responsible for collecting and accurately recording the data generated for this trial.
- 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 trial 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 trial, and other trial-related aspects requested by the EC, Competent Authority or Sponsor representative. (These are described in more detail in the Investigator Agreement.)

The Sponsor reserves the right to terminate this study at a given site or across all sites if any of the following situations occur:

- The rate at which patients are being entered into the study is insufficient as determined by the Sponsor;

- Protocol compliance is poor as measured by the number of reported and monitored protocol deviations and violations;
- Data recording is inaccurate or incomplete on a chronic basis;
- The incidence and/or severity of adverse events related to the use of the study device indicate a potential increased risk to the safety and welfare of trial patients;
- The Sponsor and/or the local Competent Authority mandate the termination of the study.

### Study Coordinator

Each site in the Mitral TRACER Trial 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 trial and those who have entered the trial 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 trial site(s) shall be monitored in accordance with policies at Harpoon Medical, Inc. and those federal regulations that pertain to clinical research; namely, ISO-14155, 21 CFR Parts 50, and 56; and others as applicable.

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial. 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 Principal Investigator and staff.

During the course of the investigation, the Monitor shall assure that the Principal Investigator 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 Patient Information Sheet approved by the REC;
- 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 approved by the ethics committee and reported to Sponsor, Inc. and the EC;
- Adverse events (anticipated and unanticipated) are recorded and reported in accordance with the spirit of Good Clinical Practices (GCPs), ISO-14155-1, 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 dealt with in the usual confidential fashion. 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.

#### CLINICAL ENDPOINT COMMITTEE

A Clinical Endpoint Committee (CEC) is responsible for adjudicating all SAEs including device deficiencies which may lead to SAE through the 36 month follow-up. In addition all confirmed SAEs are assessed in regards to relationship to the Harpoon device and Index procedure.

The Sponsor's Safety Department manages all CEC preparation activities according to an approved CEC Charter.

Adjudicated data is used for a final analysis. If event is not adjudicated, site reported data is used.

#### STUDY ADMINISTRATION

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

#### **Source Documentation**

The Investigator must maintain detailed source documents on all trial patients who are enrolled in the trial or who undergo screening. Source documents include patient medical records, hospital charts, clinic charts, Investigator's patient trial files, as well as the results of diagnostic tests (e.g.,

laboratory tests) 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.

The following minimum information should be recorded in the patient's medical records:

- The date the patient entered the trial and the patient number
- The trial protocol number and the name of the Sponsor
- The date that informed consent was obtained
- Evidence that the patient meets trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations)
- The dates of all trial related patient visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the patient exited the trial, and a notation as to whether the patient completed the trial or was discontinued, including the reason for discontinuation

### **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**

Harpoon Medical, Inc. reserves the right to stop the screening of patients at a study center at any time after the study initiation visit if no patients have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

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
- Loss of (or unaccounted for) investigational product inventory

### **Protocol Deviations and Violations**

A protocol deviation is defined as an accidental or unintentional changes to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a

significant effect on the patient's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the patient, researcher, or research staff.

A deviation may be due to the research patient's non-adherence, or an unintentional change to or non-compliance with the research protocol on the part of a researcher.

**Protocol Violation** is a divergence from the protocol that materially reduces the quality or completeness of the study data, makes the Informed Consent Form inaccurate, or materially impacts a patient's safety, rights, or welfare.

Investigators are required to obtain prior approval from MedPass Limited before knowingly deviating from the protocol, except where necessary to protect the life or physical well-being of a patient in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., patient was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Protocol deviations and violations must be reported to the Sponsor regardless of whether medically justifiable, pre-approved by MedPass Limited or taken to protect the patient in an emergency. Patient specific deviations will be reported on the Protocol Deviation case report form. Non-patient specific deviations, (e.g., unauthorised use of an investigational device outside the study, unauthorised use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to Harpoon Medical. Investigators are also required to report deviations and violations to their EC and CA, where required, in accordance with their specific reporting policies and procedures. Copies of these reports should be maintained in the site regulatory binder and will be reviewed by the Monitor.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from and violation of the protocol.

## 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 trial.

### **Site**

The Sponsor and clinical sites will maintain all records pertaining to this study for a period of seven years following the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a regulatory submission. If the reviewing Ethics Committee or Competent Authority retention policy is longer than seven years, record retention will be mandated under those respective policies. Record retention dates will be provided to all concerned by the Sponsor.

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

A center may initiate enrollment in the Mitral TRACER Trial 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 enrollment 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 communications will be kept in the regulatory communication binder at each participating site.

## DATA QUALITY ASSURANCE

Case Report Forms specific to the Mitral TRACER Trial 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 CRFs will be collected by MedPass Limited and entered 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.

## SPONSOR

The responsibilities of the Sponsor include obtaining regulatory and local approvals before the start of the trial, obtaining liability insurance according to local regulations, obtaining the signed Investigator's Agreements, reviewing significant new trial-related information, reporting unanticipated adverse events to the authorities in accordance with the Sponsor's Quality Procedures, maintaining copies of correspondence, data, shipment of product and other records related to the clinical trial. The Sponsor may delegate one or all of these tasks; however, it remains the Sponsor's responsibility to adequately supervise any designee acting on their behalf to ensure compliance to all applicable procedures, laws and regulations.

## STATEMENT OF INSURANCE POLICY

Harpoon Medical, Inc. shall, at its own expense, carry and maintain professional and general liability insurance from a carrier in amounts sufficient to cover the indemnification obligations assumed hereunder, but in no event less than \$500,000 per occurrence and \$5 million in the aggregate. Harpoon Medical, Inc. shall provide evidence of insurance to the investigational site promptly upon execution of the Investigator Agreement.



## 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 should be forwarded to MedPass and Sponsor for review and approval, and 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 trial, 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 and time 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 trial 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 may initiate enrollment in the Mitral TRACER Trial 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:

1. Be appropriately trained on the use of the Harpoon Medical device and procedure.
2. Be willing to change their clinical / surgical routine if required by the protocol.
3. Have an adequate medical Ethics Committee and be willing to comply with Good Clinical Practice, and the European standard EN 540 for the conduct of clinical investigations of medical devices.
4. 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.
5. Be willing to allow clinical monitors to enter at reasonable times for inspection of all records pertaining to the trial.

#### **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 the Mitral TRACER trial on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

Sponsor commits to seek publication of results of its completed applicable clinical trials on any product that receives CE Mark in the peer-reviewed scientific literature, regardless of trial outcome. Sponsor supports recognised 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 the Mitral TRACER Trial. 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 Principal Investigator 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 Principal Investigator.

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, Principal Investigator 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 Principal Investigator. Sponsor shall have the right to request modification of any Publication if in Sponsor's reasonable opinion such Publication will jeopardise 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 statistical 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 the Mitral TRACER Trial or a subset

analysis of any patients enrolled in the Mitral TRACER Trial, 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 trial 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 recognised in acknowledgments when the manuscript is published. In some cases, journals recognise 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.

## XV. REFERENCES

ClinicalTrials.gov registry number: NCT01777815: [Safety and Performance Study of the NeoChord Suturing Device in Subjects With Degenerative Mitral Valve Disease; Diagnosed With Severe Mitral Regurgitation](#)

ClinicalTrials.gov registry number: NCT01784055: [Post-Market Surveillance Registry for the NeoChord DS1000](#)

[Artificial chordae for degenerative mitral valve disease: critical analysis of current techniques](#)

Ibrahim M, Rao C, Athanasiou T.

Interact Cardiovasc Thorac Sur 2012 Dec; 15(6): 1019-32 Epub 2012 Sep

[Mitral Valve Repair, a Clinical and Echocardiographic Study](#)

Xu M, McHaffieDJ, Hilless AD.

Br Heart J 1994 Jan; 71(1):51-6

[A simple approach to mitral valve repair, posterior leaflet height adjustment using a partial fold of the free edge](#)

Abicht TO, Andrei AC, Druse J, McDonald E, Li Z, McCarthy PM

J Thoracic Cardiovasc Surg. 2014 Dec; 148(6): 2780-6 Epub 2014 Jul 22

[Transapical Beating Heart Mitral Valve Repair.](#)

Seeburger J, Borger MA, Tschernich H, Leontjev S, Holzhey D, Noack T, Ender J, Mohr FW.:

Circulation Cardiovascular Interventions. 2010; 3: 611-612

[Transapical neochord implantation.](#)

Seeburger J, Winkfein M, Höebartner M, Noack T, Kiefer P, Vollroth M, Leontjev S, Mohr FW.

Multimedia Manual of Cardiothoracic Surgery. doi:10.1510/mmcts.2010.004606

[Off-pump transapical implantation of artificial chordae to correct mitral regurgitation: Early results of a single-center experience.](#)

Rucinskas K, Janusauskas V, Zakarkaite D, Aidietiene S, Samalavicius R, Speziali G, Aidietis A.

J Thorac Cardiovasc Surg. 2014 Jan;147(1):95-9. doi: 10.1016/j.jtcvs.2013.08.012. Epub 2013 Oct 5.

[Off pump transapical implantation of artificial chordae to correct mitral regurgitation \(TACT trial\) - proof of concept.](#)

Seeburger J, Rinaldi M, Nielsen SL, Salizone S, Lange R, Schoenburg M, Alfieri O, Borger MA, Mohr FW, Aidietis K.

J Am Coll Cardiol. 2014 Mar 11;63(9):914-9. doi: 10.1016/j.jacc.2013.07.090. Epub 2013 Sep 24

[Transapical neochord implantation: Is tension of artificial chordae tendinae dependent on the insertion site?](#)

Jensen H, Jensen MO, Waziri F, Honge JL, Sloth E, Fenger-Gron M, Nielsen SL.

J Thorac Cardiovasc Surg. 2013 Sep 13. pii: S0022-5223(13)00901-X. doi: 10.1016/j.jtcvs.2013.07.068. [Epub ahead of print]

[Early rupture of an expanded polytetrafluoroethylene neochord after complex mitral valve repair: an electron microscopic analysis.](#)

Castillo JG, Anyanwu AC, El-Eshmawi A, Gordon RE, Adams DH.

J Thorac Cardiovasc Surg. 2013 Mar;145(3):e29-31. doi: 10.1016/j.jtcvs.2012.12.011. Epub 2013 Jan 12. No abstract available.

[Innovations in minimally invasive mitral valve pair.](#)

Sündermann SH, Seeburger J, Scherman J, Mohr FW, Falk V.

Surg Technol Int. 2012 Dec;22:207-12.

[Chordal relocation for repair of anterior mitral leaflet flail: a reproducible option.](#)

Schaheen LW, Hayanga AJ, Badhwar V.

Multimed Man Cardiothorac Surg. 2014 Jan 1;2014(0):mmt021. doi: 10.1093/mmcts/mmt021.

[Tirone David valve-sparing aortic root replacement and cusp repair for bicuspid aortic valve disease.](#)

Kari FA, Liang DH, Kvitting JP, Stephens EH, Mitchell RS, Fischbein MP, Miller DC.

J Thorac Cardiovasc Surg. 2013 Mar;145(3 Suppl):S35-40.e1-2. doi: 10.1016/j.jtcvs.2012.11.043. Epub 2012 Dec 20.

[Augmented reality image guidance improves navigation for beating heart mitral valve repair.](#)

Chu MW, Moore J, Peters T, Bainbridge D, McCarty D, Guiraudon GM, Wedlake C, Lang P, Rajchl M, Currie ME, Daly RC, Kiaii B.  
Innovations (Phila). 2012 Jul-Aug;7(4):274-81. doi: 10.1097/IMI.0b013e31827439ea.

A navigation platform for guidance of beating heart transapical mitral valve repair.

Moore JT, Chu MW, Kiaii B, Bainbridge D, Guiraudon G, Wedlake C, Currie M, Rajchl M, Patel RV, Peters TM.  
IEEE Trans Biomed Eng. 2013 Apr;60(4):1034-40. doi: 10.1109/TBME.2012.2222405. Epub 2012 Oct 3.

Trans-apical beating-heart implantation of neo-chordae to mitral valve leaflets: results of an acute animal study.

Seeburger J, Leontjev S, Neumuth M, Noack T, Höbartner M, Misfeld M, Borger MA, Mohr FW.  
Eur J Cardiothorac Surg. 2011 May 17

Trans-apical beating-heart implantation of neo-chordae to mitral valve leaflets: results of an acute animal study.

Seeburger J, Leontjev S, Neumuth M, Noack T, Höbartner M, Misfeld M, Borger MA, Mohr FW.  
Eur J Cardiothorac Surg. 2012 Jan;41(1):173-6; discussion 176. doi: 10.1016/j.ejcts.2011.03.058.

Off pump transapical implantation of artificial chordae to correct mitral regurgitation (TACT trial) - proof of concept.

Seeburger J, Rinaldi M, Nielsen SL, Salizone S, Lange R, Schoenburg M, Alfieri O, Borger MA, Mohr FW, Aiditeis K.  
J Am Coll Cardiol. 2013 Sep 17. pii: S0735-1097(13)05160-7. doi: 10.1016/j.jacc.2013.07.090. [Epub ahead of print]

Transapical neochord implantation.

Seeburger J, Winkfein M, Höbartner M, Noack T, Kiefer P, Vollroth M, Leontjev S, Mohr FW.  
Multimedia Manual of Cardiothoracic Surgery. doi:10.1510/mmcts.2010.004606

Acute safety and efficacy of the NeoChord Procedure

A, Manzan E, Rucinkas K, Janusauskas V, Zucchetta F, Zakarkaite D et al..  
Interact CardioVasc Thorac Surg 2015; doi:10.1093/icvts/ivv014.

Burden of valvular heart diseases: a population-based study. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Lancet 2006;3681005-11.

Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals  
International Committee of Medical Journal Editors (ICMJE). [Accessed September 17, 2013]

Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography (Zoghbi et al, J Am Soc Echocardiography 2003; 16:777-802)

## **APPENDIX A: DECLARATION OF HELSINKI**

### Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964  
and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

### Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

### General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

#### Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.



18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

### Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

### Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

### Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

## Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

## Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the

study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

#### Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

#### Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

#### Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

### Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.