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Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

National foreword

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Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

*Implants cardiovasculaires et circuits extra-corporels — Dispositifs de
réparation de valves cardiaques*





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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

Introduction

No heart valve repair device is ideal. Therefore, a group of engineers, scientists, and clinicians, experts well aware of the problems associated with heart valve repair devices and their development, has prepared this document. This document specifies types of tests, test methods, and requirements for test apparatus. It requires documentation of test methods and results. This document deals with those areas that will ensure adequate mitigation of device-associated risks for patients and other users of the device, facilitate quality assurance, aid the heart team in choosing a heart valve repair device, and ensure that the device will be provided in a convenient and usable form. This document emphasizes the need to specify and report types of *in vitro* testing, preclinical *in vivo* and clinical evaluations. It describes the labels and packaging of the device. Such a process involving *in vitro*, preclinical *in vivo* and clinical evaluations is intended to clarify the requirements prior to market release and to enable prompt identification and management of any subsequent problems.

With regard to *in vitro* testing and reporting, apart from basic material testing for mechanical, physical, chemical and biocompatibility characteristics, this document also covers important functional and durability characteristics of heart valve repair devices and their accessories. This document does not specify exact test methods for functional and durability testing but it offers guidelines for the test apparatus.

This document should be revised, updated, and amended as knowledge and techniques in heart valve repair device technology improve.

Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

1 Scope

1.1 This document applies to all heart valve repair systems that have an intended use to repair and/or improve the function of native human heart valves by acting either on the valve apparatus or on the adjacent anatomy (e.g. ventricle, coronary sinus).

1.2 This document outlines an approach for verifying/validating the design and manufacture of a heart valve repair system through risk management. The selection of appropriate verification/validation tests and methods are derived from the risk assessment. The tests include assessments of the physical, chemical, biological, and mechanical properties of components and materials of heart valve repair systems. The tests also include preclinical *in vivo* evaluation and clinical investigation of the finished heart valve repair system to assess the safety and effectiveness of the heart valve repair system.

NOTE For the purposes of this document, effectiveness endpoint includes clinical performance and benefits.

1.3 This document defines operational conditions and performance requirements for heart valve repair systems where adequate scientific and/or clinical evidence exists for their justification.

1.4 This document excludes Cardiac Resynchronization Therapy (CRT) devices, paravalvular leakage closure devices, systems that do not leave an implant in place (e.g. ablation, radio frequency annuloplasty), apical conduits and devices with components containing viable cells. This Standard also excludes materials not intended for repairing and/or improving the function of human heart valves according to its intended use (e.g. patch material and sutures used in general surgical practice).

NOTE A rationale for the provisions of this document is given in [Annex A](#).

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 11135, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14160, *Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices*

ISO 14630, *Non-active surgical implants — General requirements*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 15223-2, *Medical devices — Symbols to be used with medical device labels, labelling, and information to be supplied — Part 2: Symbol development, selection and validation*

ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories*

ISO 17664, *Processing of health care products — Information to be provided by the medical device manufacturer for the processing of medical devices*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO/TS 17665-2, *Sterilization of health care products — Moist heat — Part 2: Guidance on the application of ISO 17665-1*

ISO/TS 17665-3, *Sterilization of health care products — Moist heat — Part 3: Guidance on the designation of a medical device to a product family and processing category for steam sterilization*

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

ISO/TR 22442-4, *Medical devices utilizing animal tissues and their derivatives — Part 4: Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes*

IEC 62366-1, *Medical devices — Part 1: Application of usability engineering to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

- IEC Electropedia: available at <http://www.electropedia.org/>
- ISO Online browsing platform: available at <https://www.iso.org/obp>

NOTE Additional definitions can be found in the informative annexes.

3.1

abnormal use

act or omission of an act by the operator or user of a medical device as a result of conduct which is beyond any means of risk control by the manufacturer

3.2

accessory

device-specific tool that is required to assist in the implantation and/or adjustment of the heart valve repair device, excluding the delivery system

3.3

active comparator

active control

intervention generally accepted or demonstrated to be safe and effective for the condition of interest that can be used as a basis of comparison of the safety and effectiveness of the heart valve repair device

Note 1 to entry: The active comparator is generally the standard of care for the condition.

3.4

actuarial analysis

statistical technique for calculating event rates over time

Note 1 to entry: Standard actuarial methods calculate the probability of freedom from events within pre-specified intervals of time. When the intervals approach zero width, the methods are called Kaplan-Meier methods.

3.5

adverse event

AE

untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the heart valve repair device implantation, adjustment or procedure

3.6

auxiliary device

device used during the procedure, not including accessories (e.g. sheath, guidewire) and delivery system

3.7

back pressure

differential pressure applied across the valve during the closed phase

3.8

body surface area

BSA

total surface area (m^2) of the human body

Note 1 to entry: This can be calculated as the square root of product of the weight in kg times the height in cm divided by 3 600. See Reference [30].

3.9

cardiac index

cardiac output ([3.10](#)) (CO, l/min) divided by the *body surface area* ([3.8](#)) (BSA, m^2), with units l/min/ m^2

3.10

cardiac output

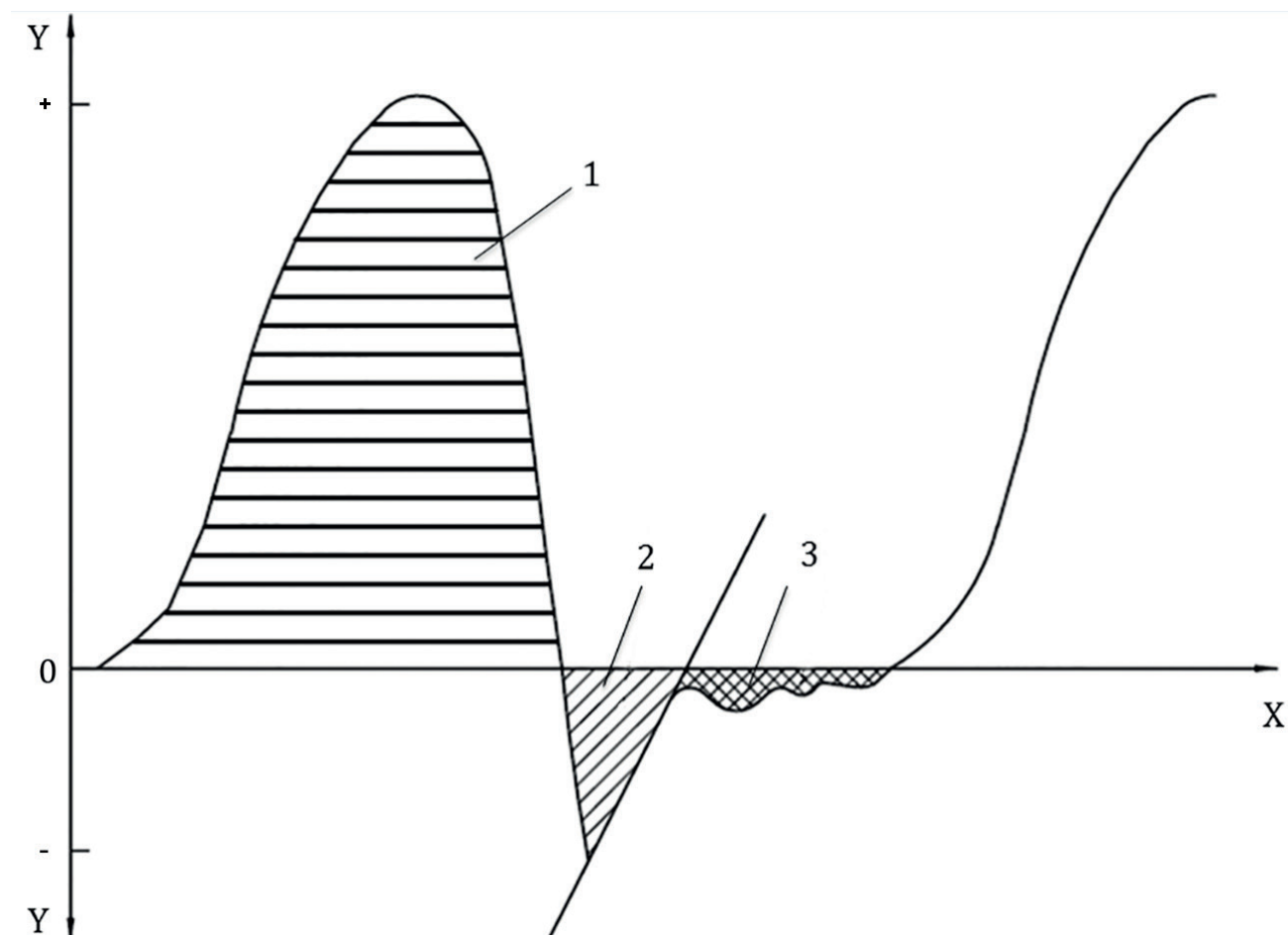
CO

stroke volume multiplied by heart rate

3.11 closing volume

portion of the regurgitant volume that is associated with the dynamics of the valve closure during a single cycle

Note 1 to entry: See [Figure 1](#).



Key

- X time
- Y flowrate
- 1 forward flow volume
- 2 closing volume
- 3 leakage volume

Figure 1 — Schematic representation of flow waveform and regurgitant volumes for one cycle

3.12 coating

thin-film material that is applied to an element of a heart valve repair device to modify its properties

3.13 compliance

relationship between change in radius and change in pressure of a deformable tubular structure (e.g. valve annulus, aorta, conduit), defined in this document as:

$$C = 100 \% \times \frac{(r_2 - r_1) \times 100}{r_1 \times (p_2 - p_1)}$$

where

C is the compliance in units of % radial change/100 mmHg;

p_1 is the diastolic pressure, in mmHg;

p_2 is the systolic pressure, in mmHg;

r_1 is the inner radius at p_1 , in millimetres;

r_2 is the inner radius at p_2 , in millimetres.

Note 1 to entry: See Reference [7].

3.14

component-joining material

material, such as a suture, adhesive or welding compound, used to assemble the components of a heart valve repair device, thereby becoming part of the implanted device

3.15

cycle

one complete sequence in the action of a heart valve under pulsatile flow conditions

3.16

cycle rate

number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)

3.17

delivery system

system used to deliver, deploy, attach or adjust the device in the implant site

3.18

design validation

establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.34)

3.19

design verification

establishment by objective evidence that the design output meets the design input requirements

3.20

device embolisation

dislodgement from the intended and documented original position to an unintended and nontherapeutic location

3.21

device failure

inability of a device to perform its intended function sufficient to cause a hazard

3.22

device migration

unintended movement or displacement of the device from its original position within the implant site, without embolisation

3.23
effective orifice area
EOA

orifice area that has been derived from flow and pressure or velocity data

Note 1 to entry: For *in vitro* testing, EOA is defined as:

$$EOA = \frac{q_{v_{RMS}}}{51,6 \times \sqrt{\frac{\Delta p}{\rho}}}$$

where

EOA is the effective orifice area (cm²);

$q_{v_{RMS}}$ is the root mean square forward flow (ml/s) during the positive differential pressure period;

Δp is the mean pressure difference (measured during the positive differential pressure period) (mmHg);

ρ is the density of the test fluid (g/cm³).

3.24
failure mode

mechanism of *device failure* ([3.21](#))

3.25
follow-up

continued assessment of subjects who have received the heart valve repair device

3.26
forward flow volume

volume of flow ejected through the heart valve in the forward direction during one cycle, not including any regurgitant flow through the valve

Note 1 to entry: See [Figure 1](#).

3.27
fracture

complete separation of any part of the *heart valve repair device* ([3.28](#)) that was previously intact

3.28
heart valve repair device

implant ([3.31](#)) intended to improve the function of native human heart valves by acting either on the valve apparatus or on the adjacent anatomy (e.g. ventricle, coronary sinus)

Note 1 to entry: See examples in [Annex B](#).

3.29
heart valve repair system

heart valve repair device, delivery system, other accessories as applicable, packaging, labelling, and instructions

3.30
imaging modality

method used to visualize and assess native anatomy and/or device position, geometry and/or function

3.31
implant

device placed surgically or non-surgically into the human body and intended to remain in place after the procedure

3.32**implant site**

location of heart valve repair device implantation or deployment

3.33**indication for use**

clinical condition of the patient population that the heart valve repair device is intended to treat or improve

3.34**intended use**

purpose of a heart valve repair device, in accordance with the specifications, instructions, and information provided by the manufacturer

3.35**Kaplan-Meier methods**

statistical approaches to calculating event rates over time when the actual dates of events for each person in the population are taken into account

3.36**leakage volume**

component of the regurgitant volume that is associated with leakage during closed phase of a valve in a single cycle

Note 1 to entry: See [Figure 1](#). The point of separation between the closing and leakage volumes is obtained according to a defined and stated criterion (the linear extrapolation shown in [Figure 1](#) is just an example).

3.37**linearized rate**

total number of events divided by the total time under evaluation

Note 1 to entry: Generally, the rate is expressed in terms of percent per patient year.

3.38**mean arterial pressure**

time-averaged arithmetic mean value of the arterial pressure during one cycle

3.39**mean pressure difference**

time-averaged arithmetic mean value of the pressure difference across a heart valve during the positive differential pressure period of the cycle

Note 1 to entry: See [Figure 2](#) for representative aortic and mitral flow and pressure waveforms. See [Figure 3](#) for representative pulmonary and tricuspid flow and pressure waveforms.

3.40**non-structural dysfunction**

abnormality extrinsic to the heart valve repair device that results in abnormal function of the device or causes clinical symptoms

3.41**pannus**

ingrowth of tissue onto the heart valve repair device which may interfere with normal functioning

3.42**pull-out**

situation in which the suture or anchoring device remains structurally intact but tears through the tissue in which it is implanted

3.43

reference device

heart valve substitute or heart valve repair device with known clinical history used for comparative preclinical and clinical evaluations

3.44

regurgitant fraction

regurgitant volume expressed as a percentage of the total ventricular stroke volume

3.45

regurgitant volume

volume of fluid that flows through a heart valve in the reverse direction during one cycle and is the sum of the closing volume and *leakage volume* (3.36)

Note 1 to entry: See [Figure 1](#).

3.46

repositioning

intentional change of implant position of a partially or fully deployed heart valve repair device

3.47

retrieval

removal of a partially or fully deployed heart valve repair device

3.48

risk

combination of the probability of occurrence of harm and the *severity* (3.53) of that harm

Note 1 to entry: See ISO 14971.

3.49

risk analysis

systematic use of available information to identify hazards and to estimate the associated *risks* (3.48)

Note 1 to entry: See ISO 14971.

3.50

risk assessment

overall process comprising a *risk analysis* (3.49) and a risk evaluation

Note 1 to entry: See ISO 14971.

3.51

root mean square forward flow

RMS forward flow

square root of the integral of the volume flow rate waveform squared during the positive differential pressure interval of the forward flow phase used to calculate EOA

Note 1 to entry: Defining the time interval for flow and pressure measurement as the positive pressure period of the forward flow interval for EOA computation provides repeatable and consistent results for comparison to the minimum device performance requirements.

Note 2 to entry: This is calculated using the following equation:

$$q_{v_{RMS}} = \sqrt{\frac{\int_{t_1}^{t_2} q_v(t)^2 dt}{t_2 - t_1}}$$

where

$q_{v_{RMS}}$ is the root mean square forward flow (ml/s) during the positive differential pressure period;

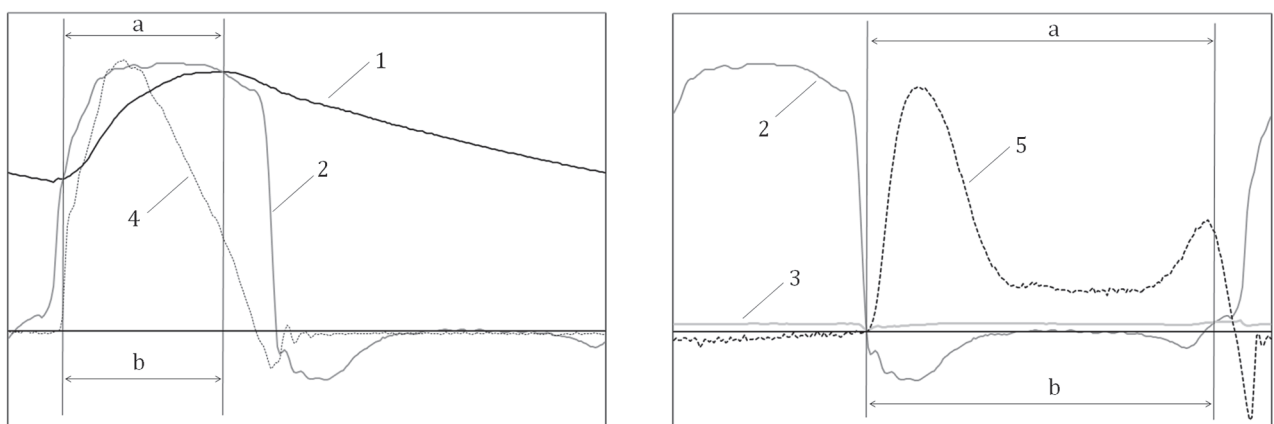
$q_v(t)$ is the instantaneous flow at time t ;

t_1 is time at start of positive differential pressure period;

t_2 is time at end of positive differential pressure period.

Note 3 to entry: The rationale for use of $q_{v_{RMS}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate, and it is the mean pressure difference that is required.

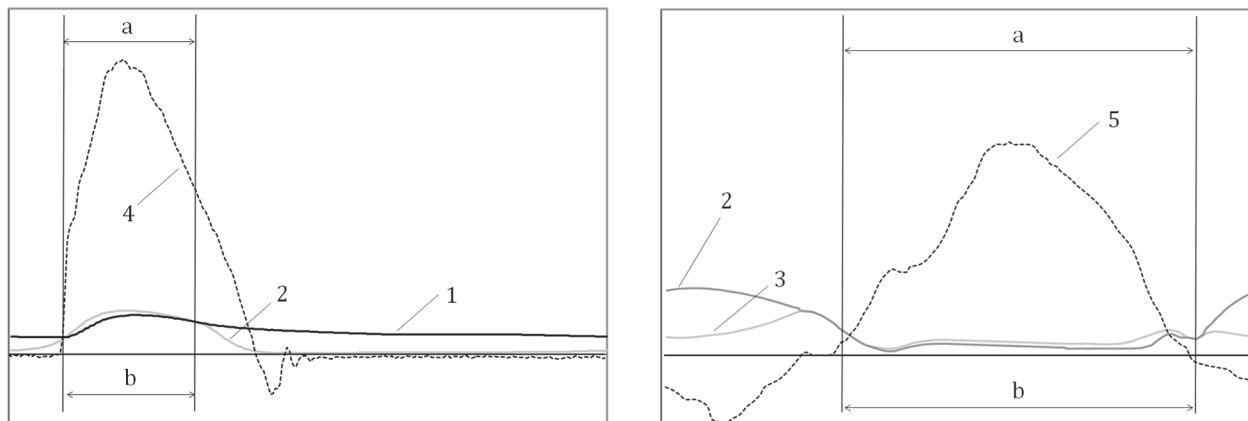
Note 4 to entry: See [Figure 2](#) for representative aortic and mitral flow and pressure waveforms from *in vitro* testing. See [Figure 3](#) for representative pulmonary and tricuspid flow and pressure waveforms from *in vitro* testing.



Key

- 1 aortic pressure
- 2 left ventricular pressure
- 3 left atrial pressure
- 4 aortic flow rate
- 5 mitral flow rate
- a Positive pressure range.
- b $q_{v_{RMS}}$ range.

Figure 2 — Schematic representation of aortic and mitral flow and pressure waveforms versus time from *in vitro* testing



Key

- 1 pulmonary pressure
- 2 right ventricular pressure
- 3 right atrial pressure
- 4 pulmonary flow rate
- 5 tricuspid flow rate
- a Positive pressure range.
- b q_{vRMS} range.

Figure 3 — Schematic representation of pulmonary and tricuspid flow and pressure waveforms versus time from *in vitro* testing

3.52

safety

freedom from unacceptable risk

Note 1 to entry: See ISO 14971.

3.53

severity

measure of the possible consequences of a hazard

Note 1 to entry: See ISO 14971.

3.54

simulated cardiac output

forward flow volume multiplied by heart rate

Note 1 to entry: Simulated cardiac output applies to *in vitro* bench testing only in this document.

3.55

special process

process for which the product cannot be fully verified by inspection or test

3.56

sterility assurance level

SAL

probability of a single viable microorganism occurring on an item after sterilization

Note 1 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3} . When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3} .

Note 2 to entry: See Reference [6].

3.57

sterilization

validated process used to render product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: See Reference [6].

3.58

stroke volume

SV

volume of blood pumped by a ventricle in one contraction, which is equal to the difference between the end diastolic ventricular volume and end systolic ventricular volume

3.59

structural device or component failure

degradation of structural integrity of the repair device (e.g. fractures) that results in the functional performance of the implant no longer being acceptable and/or that results in *adverse events* (3.5)

3.60

structural native valve deterioration

structural native valve dysfunction

dysfunction or deterioration intrinsic to the native valve, including calcification, leaflet fibrosis, leaflet tear or flail, resulting in stenosis or intra-prosthetic regurgitation

3.61

systolic duration

portion of cardiac cycle time corresponding to ventricular contraction

Note 1 to entry: For *in vitro* testing, systolic duration corresponds to the duration of forward flow in a cardiac cycle.

3.62

total product life cycle

period of time over which a product is developed, brought to market and eventually removed from the market

3.63

usability

characteristic of the user interface that facilitates use and thereby establishes effectiveness, efficiency, ease of user learning and user satisfaction in the intended use environment

3.64

use error

act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

Note 1 to entry: Examples of use error include incorrect sizing, suboptimal positioning, structural distortion of the device.

Note 2 to entry: An unexpected physiological response of the patient is not by itself considered use error.

4 Abbreviations

For the purposes of this document, the following abbreviations apply.

AE	adverse event
AWT	accelerated wear testing
CO	cardiac output
CT	computed tomography
CIP	clinical investigation plan
CFD	computational fluid dynamics
ECG	electrocardiogram
EOA	effective orifice area
FEA	finite element analysis
IFU	instructions for use
INR	international normalized ratio
LV	left ventricle, left ventricular
MAP	mean arterial pressure
MRI	magnetic resonance imaging
PET	positron emission tomography
PMCF	post-market clinical follow-up
SV	stroke volume
TEE	transoesophageal echocardiography
TTE	transthoracic echocardiography

5 Fundamental requirements

5.1 General

The manufacturer shall determine, at all stages of the total product life cycle, the acceptability of the product for clinical use.

5.2 Risk management

Risk management is the essential element for design and verification of medical devices. A risk-based methodology challenges the manufacturer to continually evaluate known and theoretical risks of the device, to develop the most appropriate methods for mitigating the risks of the device, and to implement the appropriate test and analysis methods to demonstrate that the risks have been mitigated. The manufacturer shall define, implement and document risk management activities in accordance with ISO 14971. The risk analysis shall be an iterative process over the total product life cycle of the device based on evolving knowledge of device performance. [Annex G](#) outlines a risk management approach relevant to heart valve repair devices, and provides examples of potential approaches to risk management. In addition, a list of potential hazards specific to the various types of heart valve repair devices that can serve as the basis for a risk analysis is also provided.

6 Device description

6.1 Intended use/Indication for use

The manufacturer shall identify the pathophysiological condition(s) to be treated, the intended patient population, and intended claims.

6.2 Design inputs

6.2.1 General

The design attribute requirements of ISO 14630 shall apply.

6.2.2 Operational specifications

The manufacturer shall define the operational specifications for the system, including the principles of operation, intended device delivery approach if applicable, expected device lifetime, shelf life, shipping/storage limits, and the physiological environment in which it is intended to function. The manufacturer shall define all relevant dimensional parameters that will be required to accurately select the size of device to be implanted, if applicable. [Table 1](#) and [Table 2](#) define the expected physiological parameters of the intended adult patient population for heart valve repair devices for both normal and pathological patient conditions. See [Annex H](#) for guidelines regarding suggested test conditions for the paediatric population.

Table 1 — Heart valve repair device operational environment for left side of heart — Adult population

Parameter	General Condition			
Surrounding medium	Human heart/Human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 bpm to 200 bpm			
Cardiac output	3 l/min to 15 l/min			
Forward flow volume	25 ml to 100 ml			
Pressures and resultant pressure loads by patient condition	Aortic peak systolic pressure mmHg	Aortic end diastolic pressure mmHg	Peak differential pressure across closed valve ^a	
			Aortic ΔP_A mmHg	Mitral ΔP_M mmHg
Normotensive	90 to 140	60 to 90	80 to 115	90 to 140
Hypotensive	<90	<60	<80	<90
Mild hypertensive	140 to 159	90 to 99	115 to 129	140 to 159
Moderate hypertensive	160 to 179	100 to 109	130 to 144	160 to 179
Severe hypertensive	180 to 209	110 to 119	145 to 164	180 to 209
Very severe hypertensive	≥210	≥120	≥165	≥210
^a Peak differential pressure across closed aortic valve estimated using the following relationship: — $\Delta P_A \approx$ pressure associated with dicrotic notch assuming LV pressure is zero $\approx$ Aortic end diastolic pressure + $\frac{1}{2}$ (Aortic peak systolic pressure – Aortic end diastolic pressure). Peak differential pressure across closed mitral valve estimated to be equivalent to Aortic peak systolic pressure. Pressure values obtained from references (See references [28] , [33]).				

Table 2 — Heart valve repair devices operational environment for right side of heart – Adult population

Parameter	General Condition			
Surrounding medium	Human heart/Human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 bpm to 200 bpm			
Cardiac output	3 l/min to 15 l/min			
Forward flow volume	25 ml to 100 ml			
Pressures and resultant pressure loads by patient condition	Pulmonary artery peak systolic pressure mmHg	Pulmonary artery end diastolic pressure mmHg	Peak differential pressure across closed valve ^a	
			Pulmonary ΔP_P mmHg	Tricuspid ΔP_T mmHg
Normotensive	18 to 35	8 to 15	13 to 28	18 to 35
Hypotensive	<18	<8	<13	<18
Mild hypertensive	35 to 49	15 to 19	28 to 34	35 to 49
Moderate hypertensive	50 to 59	20 to 24	35 to 42	50 to 59
Severe hypertensive	60 to 84	25 to 34	43 to 59	60 to 84
Very severe hypertensive	≥85	≥35	≥60	≥85
^a Peak differential pressure across closed pulmonary valve estimated using the following relationship: — $\Delta P_P \approx$ pressure associated with dicrotic notch assuming RV pressure is zero $\approx$ Pulmonary artery end diastolic pressure + $\frac{1}{2}$ (Right ventricle peak systolic pressure – Pulmonary artery end diastolic pressure). — Peak differential pressure across closed tricuspid valve estimated to be equivalent to Pulmonary artery peak systolic pressure.				

6.2.3 Functional, performance and safety requirements

6.2.3.1 General

The manufacturer shall establish (i.e. define, document, and implement) the functional, performance and safety requirements of the heart valve repair system. With valve replacement devices, haemodynamic performance and those adverse events which are directly valve-related can be measured and reasonably attributed predominantly to the device. In contrast, because valve repair devices modify the native valve or its function, leaving the native valve leaflets in place, haemodynamic and clinical performance including adverse events can also depend on factors relating to the native valve and factors other than the device itself. See 7.4.2 for examples of such factors.

6.2.3.2 Implantable device

The intended performance of the heart valve repair device shall take into consideration at least the following:

- the ability to repair valve function;
- the ability to resist migration and embolisation;
- the ability to minimize haemolysis;
- the ability to minimize thrombus formation;
- biocompatibility;
- the ability to resist corrosion;
- compatibility with adjacent structures or other implanted devices;

- h) compatibility with diagnostic imaging techniques (e.g. MRI);
- i) visibility under diagnostic imaging techniques (e.g. MRI, echocardiography, fluoroscopy, CT);
- j) deliverability and implantability in the target population;
- k) the ability to maintain structural and functional integrity during the expected lifetime of the device;
- l) the ability to maintain structural integrity, functionality and sterility for the labelled shelf life prior to implantation;
- m) the ability to consistently, accurately and safely prepare the device for implantation;
- n) the ability to be consistently, accurately and safely implanted;
- o) the ability to be safely retrieved, adjusted and/or repositioned, if applicable.

6.2.3.3 Delivery system (if applicable)

The design attributes to meet the intended performance of the delivery system shall take into consideration at least the following:

- a) the ability to permit consistent, accurate and safe access, delivery and placement of the heart valve repair device to the intended implant site;
- b) the ability to permit consistent and safe withdrawal of the delivery system prior to and after deployment of the heart valve repair device;
- c) the ability to minimize haemolysis;
- d) the ability to minimize thrombus formation;
- e) the ability to minimize blood loss;
- f) the ability to retrieve, reposition, and/or remove the heart valve repair device (if applicable);
- g) biocompatibility;
- h) the ability to resist corrosion;
- i) the ability to avoid particulate generation;
- j) the ability to maintain its structural integrity, functionality and sterility for labelled shelf life;
- k) compatibility and visibility with diagnostic imaging techniques (e.g. MRI, echo, fluoroscopy, CT), if applicable;
- l) compatibility with other required tools and accessories that are required to complete the procedure.

6.2.4 Usability

The heart valve repair system shall provide intended users the ability to safely and effectively perform all relevant pre-operative, intra-operative, and post-operative procedural tasks and achieve all desired objectives. This shall include all procedure-specific tools and accessories that intended users will use to complete the procedure.

NOTE For guidance on how to determine and establish design attributes pertaining to the use of the system to conduct the implant procedure, see IEC 62366-1.

6.2.5 Packaging, labelling, and sterilization

The heart valve repair system shall meet the requirements for packaging, labelling, and sterilization contained within [Annex C](#), [Annex D](#), and [Annex E](#), respectively.

6.3 Design outputs

The manufacturer shall establish (i.e. define, document, and implement) a complete specification of the heart valve repair system, including component and assembly-level specifications, delivery system, accessories, packaging, and labelling. [Annex B](#) contains examples of various heart valve repair devices and [Annex F](#) contains descriptive characteristics for heart valve repair systems. In addition to the physical components of the heart valve repair system, the implant procedure itself should be considered an important element of safe and effective heart valve repair therapy.

6.4 Design transfer (manufacturing verification/validation)

The manufacturer shall generate a flowchart identifying the manufacturing process operations and inspection steps. The flowchart shall indicate the input of all components and important manufacturing materials.

As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the device is safe and suitable for its intended use. The risk management file shall identify and justify the verification/validation activities necessary to demonstrate the acceptability of the process ranges chosen.

The manufacturer shall establish the adequacy of full scale manufacturing by validation of the manufacturing process. The manufacturer shall validate all special processes and process software and document the results of the validation.

NOTE See ISO 13485.

7 Design verification testing and analysis / Design validation

7.1 General requirements

The manufacturer shall perform verification testing to demonstrate that the device specifications result in a heart valve repair system that meets the design specifications (design output meets design input). The manufacturer shall establish tests relating to hazards identified from the risk analysis. The protocols shall identify the test purpose, set-up, equipment (specifications, calibration, etc.), test conditions (with a justification of appropriateness to anticipated *in vivo* operating conditions for the device), acceptance criteria, and sample quantities tested. Test methods for verification testing shall be appropriately validated. Refer to applicable sections of ISO/IEC 17025.

The manufacturer shall validate the design of the heart valve repair system in accordance with ISO 13485 to ensure that the device specifications conform to user needs and intended use.

The requirements of this Standard are equally applicable to new or modified heart valve repair systems. For heart valve repair systems on the market prior to implementation of this Standard, and for which clinical evidence of safety and effectiveness exist, demonstration of compliance with all parts of this Standard may not be necessary. The manufacturer shall provide a justification for the lack of any such verification.

7.2 *In vitro* assessment

7.2.1 General

In vitro assessment shall be used to mitigate risks identified in the risk analysis. Design specific testing not covered herein may be required based on the findings of the risk analysis.

7.2.2 Test articles, sample selection, test conditions and reporting requirements

7.2.2.1 Test articles and sample selection

Test articles shall represent, as closely as possible, the finished heart valve repair system, including preconditioning such as exposure to the maximum number of recommended sterilization cycles, process chemicals, aging effects, shipping/ handling and any loading and deployment steps (including repositioning and recapturing, if applicable) in accordance with all manufacturing procedures and instructions for use, where appropriate. Sampling shall also ensure adequate representation of the manufacturing tolerances. Any deviations of the test articles from the finished product shall be justified.

The articles selected for testing shall fully represent all device configurations (e.g. sizes, deployment shapes, use ranges, and implant sites). Depending on the particular test, testing might not necessarily have to be completed for each device configuration. A rationale for device configuration selection shall be provided.

For all tests, the sample size shall be justified based on the specific intent of the test and risk assessment. Additional information regarding sampling and article conditioning shall be included within each test method defined herein, as appropriate.

7.2.2.2 Test conditions

The test set-up shall be representative of the critical aspects of the intended implant site (e.g. compliance, geometry, anatomical constraints, physiological interactions) for the target patient population. Variations in device deployed state shall be considered (e.g. off-axis deployment, under deployment, ellipticity) based on the risk analysis. Critical aspects of the test set-up shall be justified by the manufacturer. Test conditions shall be based on evolving knowledge of device performance in pre-clinical testing and clinical use and refined over the product life cycle of the device.

Where simulation of *in vivo* haemodynamic conditions is applicable to the test method, consideration shall be given to those operational environments given in [Table 1](#) and [Table 2](#) for the adult population. In particular, recommended pressure values provided in [Table 3](#) and [Table 4](#) shall be utilized for *in vitro* testing. See [Annex H](#) for guidelines regarding suggested test conditions for the paediatric population. Where applicable, testing shall be performed using a test fluid of isotonic saline, blood, or a blood-equivalent fluid whose physical properties (e.g. density, viscosity at working temperatures) are appropriate to the test being performed. When animal or human blood is utilized, the recommendations of ISO 10993-4 and ASTM F1830 shall be considered (see Reference [5], [11]). The testing shall be performed at the intended operating temperature as appropriate. The measurement parameters shall be defined by the manufacturer based on the design inputs.

Table 3 — Recommended pressure values for *in vitro* testing for left side of heart — Adult population

	Aortic peak systolic pressure mmHg	Aortic end diastolic pressure mmHg	Peak differential pressure across closed valve	
			Aortic ΔP_A mmHg	Mitral ΔP_M mmHg
Normotensive	120	80	100	120
Hypotensive	60	40	50	60
Mild hypertensive	150	95	125	150
Moderate hypertensive	170	105	140	170
Severe hypertensive	195	115	155	195
Very severe hypertensive	210	120	165	210

Table 4 — Recommended pressure values for *in vitro* testing for right side of heart — Adult population

	Pulmonary artery peak systolic pressure mmHg	Pulmonary artery end diastolic pressure mmHg	Peak differential pressure across closed valve	
			Pulmonary ΔP_P mmHg	Tricuspid ΔP_T mmHg
Normotensive	25	10	20	25
Hypotensive	15	5	10	15
Mild hypertensive	45	17	30	45
Moderate hypertensive	55	22	40	55
Severe hypertensive	75	30	50	75
Very severe hypertensive	85	35	60	85

7.2.2.3 Reporting requirements

Each test report shall include:

- purpose, scope and rationale for the test;
- identification and description of the heart valve repair system elements tested (e.g. batch number, size, configuration);
- identification, description and rationale for selection of the reference device(s) where appropriate;
- number of samples tested and rationale for sample size;
- detailed description of the test method including preconditioning to simulate clinical use;
- pre-specified acceptance criteria, if applicable;
- verification that appropriate quality assurance standards have been met (e.g. Good Laboratory Practice, ISO 17025);
- deviations, if any, and discussions of the effect of the deviations on the scientific validity of the test results;
- test results and conclusions (i.e. interpretation of the results).

Statistical procedures used in data analysis and rationale for their use shall be described. Test results and the conclusions shall be used as an input to the risk management documentation to assess the risk associated with a hazard/failure mode under evaluation.

7.2.3 Device material property assessment

7.2.3.1 General

Properties of the heart valve repair system components shall be evaluated as applicable to the specific design of the system as determined by the risk assessment. The materials requirements of ISO 14630 shall apply. Additional testing specific to certain materials shall be performed to determine the appropriateness of the material for use in the design.

For example, materials dependent on shape memory properties shall be subjected to testing in order to assess transformation properties.

7.2.3.2 Biological safety

The biocompatibility of the materials and components used in the heart valve repair system shall be determined in accordance with ISO 10993-1. A rationale shall be provided for the choice of data needed to evaluate each relevant potential biological effect. The test plan recorded in the risk management file shall comprise a biological safety evaluation programme with a justification for the appropriateness and adequacy of the information obtained. During the hazard identification stage of a biological safety evaluation, sufficient information shall be obtained to allow the identification of toxicological hazards and the potential for effects on relevant haematological characteristics. Where an identified hazard has the potential for significant clinical effects, the toxicological risk shall be characterized using established methods (e.g. mode of action, dose-response, exposure level, biochemical interactions, toxicokinetics).

For heart valve repair devices using animal tissue or their derivatives, the risk associated with the use of these materials shall be evaluated in accordance with the ISO 22442 series.

7.2.3.3 Material property testing

The material properties of all materials comprising the heart valve repair system shall be evaluated as applicable to its specific design and function. Characterization data from literature or engineering reports on the same materials and processing can be referenced with appropriate justification. Material properties shall be characterized for the materials of the finished device after appropriate loading and deployment, as dictated by the risk analysis. Environmental conditions that might affect material properties shall be included in testing protocols (e.g. aging). When using materials whose properties are expected to change after implantation, material property characterization shall also be conducted under relevant conditions mimicking the implantation environment (e.g. temperature, pH).

[Annex I](#) provides examples of relevant material properties by material class and components. [Annex J](#) provides a list of standards that might be applicable to the testing of materials and components. [Annex K](#) provides guidance on considerations for device material properties undergoing changes after implantation. [Annex L](#) provides guidance on corrosion assessment.

7.2.4 Functional performance assessment

An assessment of the functional performance of the device in a clinically relevant simulated repair situation shall be performed. Requirements of [7.2.2](#) shall apply. Functional assessment can be performed by means of bench, *ex vivo*, cadaver and/or computational models. A guideline for performing and reporting of functional tests is provided in [Annex M](#).

7.2.5 Device structural performance assessment

7.2.5.1 General

An assessment of the ability of the heart valve repair device to withstand the loads, deformations and/or use environments to which it will be subjected shall be performed in order to evaluate the risks associated with potential structural failure modes (e.g. fracture, tear). The structural performance assessment shall include a fatigue assessment of its individual structural components and a durability assessment of the entire device. If appropriate for the specific device design, the manufacturer shall justify situations where a single test may address both component fatigue and device durability. Structural performance assessment can be performed by means of bench testing and validated computational models.

7.2.5.2 Structural component fatigue assessment

Fatigue assessment of the individual structural components of the heart valve repair device under simulated *in vivo* conditions shall be performed in order to evaluate risks associated with fatigue-related failure modes over its anticipated *in vivo* lifetime. The assessment may be performed on sub-assemblies, individual components, and/or extracted segments of components as appropriate.

Requirements of [7.2.2](#) shall apply. The manufacturer shall determine and justify the fatigue assessment approach and associated characterization techniques utilized to best determine the fatigue lifetime for the structural components.

All load-bearing components comprising the device, including anchoring features, shall be appropriately considered. Particular aspects that can affect the anticipated *in vivo* lifetime of the heart valve repair device (e.g. tissue ingrowth, bridge therapy) shall be taken into account. It shall be demonstrated through testing and/or analysis that the structural components will remain functional for a minimum of 400 million cycles (equivalent to 10 years) for critical loading modes, unless justified when a particular device has a lower anticipated *in vivo* lifetime.

The manufacturer shall identify and justify the appropriate challenge conditions for fatigue test and analysis based on *in vivo* loading and environment. Suggested guidelines for fatigue assessment are provided in [Annex O](#).

7.2.5.3 Device durability assessment

An assessment of the durability of the entire heart valve repair device shall be performed to demonstrate reasonable assurance that the entire heart valve repair device will remain functional for a minimum of 400 million cycles (equivalent to 10 years) unless labelling includes an explicit statement about the anticipated *in vivo* device lifetime in which case testing shall be performed to support the labelling claim. The manufacturer shall provide justification if it is not feasible or appropriate to conduct *in vitro* durability testing of the entire heart valve repair device, or to test to 400 million cycles (e.g. devices with biological structural components). If testing is performed, the test setup shall be designed to be representative of critical aspects of the target implant site and loading conditions (e.g. compliance, geometry, operating temperature, pulsatile flow/pressure). Consideration shall be given to anticipated variations in the implanted device configurations. See [Annex N](#) for additional considerations.

7.2.6 Device corrosion assessment

An assessment of the corrosion resistance of the finished device and all constituent materials comprising the heart valve repair device shall be conducted. It is well established that metal corrosion potential can be sensitive to variations in manufacturing processes (e.g. heat treatment, chemical etching, electropolishing). Therefore, the corrosion resistance shall be characterized using the finished device. [Annex L](#) provides guidance on corrosion resistance characterization. The manufacturer shall provide rationale for the selected test methods and justify that all corrosion mechanisms and conditions have been considered through testing or theoretical assessments.

7.2.7 Delivery system design evaluation requirements

The manufacturer shall assess and perform tests for the delivery system as identified by the risk assessment. The delivery system may be a catheter or other device-based system used to deliver, deploy, attach or adjust the device in the implant site. [Annex U](#) provides guidelines for design evaluation requirements for delivery systems.

7.2.8 Visibility

The ability to visualize the repair device and delivery system during delivery, deployment and after delivery system withdrawal, using the manufacturer's recommended imaging modality (e.g. fluoroscopy, MRI, CT, TEE, TTE) shall be evaluated. In certain cases, the ability to directly visualize the device and delivery system may be more appropriate and shall be evaluated (e.g. surgical implantation).

7.2.9 Simulated use assessment

The ability to permit safe, consistent and accurate deployment of the heart valve repair device within the intended implant site shall be evaluated using a model that simulates the intended use conditions. Models representing the cardiac anatomy of the patient population and delivery pathway shall be considered for this assessment (e.g. isolated heart models, patient specific anatomic models). This

assessment shall include all elements of the heart valve repair device, delivery system and accessories required to facilitate delivery, deployment, adjustment and retrieval of the device, as applicable. The model shall consider anatomical variation in the intended patient population with respect to vasculature and intended implant site, temperature effects, pulsatile flow, etc. Justification for critical parameters of the simulated use model shall be provided. Potential hazards identified during simulated use testing shall be documented within the risk assessment (e.g. coronary sinus occlusion, ventricular/atrial perforation). [Annex G](#) provides guidelines for potential hazards associated with heart valve repair devices.

7.2.10 Human factors / Usability assessment

Usability assessment shall be conducted as required per the applicable sections of IEC 62366-1 to validate that intended users of the heart valve repair system can consistently deliver, deploy, adjust, reposition and retrieve the device safely and effectively. The assessment shall also focus on whether the design attributes of the heart valve repair system used to conduct the implant procedure appropriately mitigate identified potential use errors. It is recommended that usability assessment is conducted throughout the design cycle (see Reference [10]).

7.2.11 Device MRI safety

The manufacturer shall evaluate the safety and compatibility of the implant with the use of MRI. ASTM Standards F2052, F2213, F2182, F2119, and F2503 contain relevant methods of evaluation.

7.2.12 Design specific testing

Design specific testing shall be considered to assess additional failure modes identified by the risk assessment that may not have been already addressed. In some cases, design specific testing may have direct implications for the overall structural lifetime of a component or repair device, and additional tests may be required (e.g. support structure creep, static pressure test, anchoring, particulate generation, burst/circumferential strength, retrievability of device, repositionability of device, effects of device post-implantation, anatomical interactions). [Annex G](#) provides examples of potential hazards of heart valve repair devices to inform design specific testing. Examples of additional device design evaluation requirements are presented in [Annex T](#).

7.3 Preclinical *in vivo* evaluation

7.3.1 General

General requirements of ISO 14630 shall be considered.

7.3.2 Overall requirements

Preclinical studies to enable acceptably safe clinical investigations shall precede initiation of clinical investigations. An *in vivo* animal test programme shall be conducted for new or modified devices to investigate those risks and aspects of safety and effectiveness that cannot be fully evaluated from *in vitro* testing or other available data regarding heart valve repair device delivery, deployment and imaging characteristics and heart valve repair device safety and effectiveness. The preclinical programme design shall be based on the risk analysis. This programme may involve the use of different species and implant durations to address the key issues identified in the risk assessment. Use of a diseased animal model shall be considered. The choice of animal model (e.g. species, diseased or non-diseased), study duration, device size and sample size shall be justified and documented. The use of alternative implantation sites, alternative implantation techniques (e.g. transapical delivery, surgical implantation) and acute as well as chronic studies might be justified to accommodate specific heart valve repair device design features and species-specific anatomic differences. Anatomic species differences and use of diseased or non-diseased animal models shall be considered when interpreting results from preclinical *in vivo* testing alone. If a determination is made that preclinical *in vivo* evaluation is not required, justification shall be documented.

The preclinical *in vivo* evaluation shall:

- a) evaluate the extent to which the haemodynamic performance of the heart valve repair reflects the intended clinical use;
- b) assess delivery deployment, implantation procedure and imaging characteristics of the heart valve repair system. Consideration shall be given, but not limited to the following items:
 - 1) ease of use;
 - 2) delivery system handling characteristics (e.g. pushability, trackability);
 - 3) proper heart valve repair device placement and anatomic orientation;
 - 4) post-implantation changes in shape and structural components of the heart valve repair device configuration (e.g. note the presence of device angulation, bends, kinks);
 - 5) imaging characteristics;
 - 6) migration or embolisation of the heart valve repair device;
 - 7) interaction with surrounding anatomy such as leaflets, annulus and subvalvular structures;
 - 8) ability to recapture and re-deploy the heart valve repair device, if applicable;
- c) assess the *in vivo* response to the heart valve repair device. Consideration shall be given, but not limited to the following items:
 - 1) healing characteristics (e.g. pannus formation, tissue ingrowth, resorption of biodegradable materials);
 - 2) effect of post-implantation changes in heart valve repair device configuration (e.g. the presence of device angulation, bends, kinks) on functional performance;
 - 3) haemolysis;
 - 4) thrombus formation;
 - 5) embolisation of material from the implant site, delivery system or heart valve repair device;
 - 6) migration or embolisation of the heart valve repair device;
 - 7) biological response (e.g. inflammation, calcification, thrombosis, rejection, other unexpected interactions with tissues);
 - 8) interaction with surrounding anatomical structures (e.g. leaflets, annulus, subvalvular apparatus);
 - 9) structural and non-structural native valve dysfunction;
- d) use the final design of the heart valve repair device. The system shall be prepared, deployed and imaged using the same procedures (e.g. preparation of the device for delivery and deployment) as intended for clinical use. Consideration shall also be given to effects of maximum allowable conditioning steps (e.g. maximum sterilization cycles, maximum crimp time, maximum crimp cycles, etc.);

If needed, ancillary studies should be conducted to evaluate unique design and delivery aspects.

The manufacturer shall justify any modifications to the device or system that may be required for implantation in the animal model.

- e) investigate the heart valve repair device in positions for which it is intended (e.g. aortic, mitral, ventricular, coronary sinus); if species specific anatomic features or the use of a non-diseased animal model confound the ability to evaluate the heart valve repair device in positions for which

it is intended, provide a justification for implantation in an alternative site or the use of alternative implantation procedures;

- f) for comparator studies, subject the appropriate active comparator heart valve repair devices/ techniques to identical anatomic and physiological conditions as the test device;
- g) be performed by experienced and knowledgeable test laboratories, under appropriate quality assurance standards (e.g. Good Laboratory Practice);
- h) be justified and performed in accordance with the animal welfare principles provided in ISO 10993-2.

7.3.3 Methods

Guidance on the conduct of preclinical *in vivo* evaluation, and a series of tests which can be used to address the relevant issues, is provided in [Annex P](#). These studies are designed to mimic as closely as possible the clinical use of the heart valve repair device and to assess their functional performance, delivery, deployment and imaging. It is recognized that adverse events arising after device implantation can be attributed to the implanted device, the procedure, and/or the environment into which it is implanted, including interactions among these. Adverse events arising during or after device implantation shall be carefully analysed and interpreted to identify the cause of the adverse event.

The investigator should seek to control as many variables as possible within each study arm (e.g. species, gender, age). Animals suffering from complications not related to the procedure or the device (e.g. pre-existing disease) may be excluded from the group of study animals, but they shall be reported.

The number of animals used for the assessment of preclinical safety and effectiveness shall be justified based on risk assessment. For all studies, the specified duration of the observation period of the animals shall be justified according to the parameter(s) under investigation in each study protocol. For long term studies, the observation period shall not be less than 90 days.

For survival studies, a post-mortem examination shall be performed (e.g. macroscopic, radiographic, histological) focusing on device integrity and delivery system/device related pathology. The report shall include this information from all animals that have been entered into the study.

The assessment shall provide at least the following:

- a) *in vivo* evaluation of the final device design;
- b) any detectable pathological consequences, including but not limited to: migration or embolisation; changes in heart valve repair device configuration (e.g. angulations, bends, kinks); post-implantation changes in shape of structural components; thromboembolic phenomena; pannus formation; and tissue disruption and/or inflammatory responses involving the heart valve repair device and/or the major organs;
- c) any detectable structural alterations (macroscopic, microscopic or radiographic) in the heart valve repair device and macroscopic examination of the delivery system (e.g. damage, material degeneration, changes in shape or dimensions);
- d) serial blood analyses performed pre-operatively, at appropriately justified intervals during the observation period, and at termination to assess haemolysis, abnormalities in haematology and clinical chemistry parameters;
- e) delivery and deployment characteristics, including but not limited to ease of use, handling characteristics, imaging, sizing technique, retrieval and redeployment, if applicable;
- f) functional performance over a range of cardiac outputs (e.g. 2,5 to 6 l/min) in the same animal;
- g) serious adverse events, (e.g. myocardial infarction, significant cardiac arrhythmias, embolisation, native valve dysfunction);
- h) any other device or procedure related complication or events.

7.3.4 Test report

The laboratory performing the preclinical *in vivo* study shall produce the test report, which shall include a description of the risk evaluation, the complete original study protocol, all data generated from all animals of the preclinical *in vivo* evaluation necessary for the reconstruction and evaluation of the study, and a summary of the data generated during the course of the investigation, addressing the results from all animals, including serious adverse events generated from the test programme conducted in accordance with [7.2.3](#) to meet the requirements of [7.3.2](#).

The test report shall include:

- a) identification of each of the system components (delivery system, heart valve repair device, other auxiliary devices) used in the procedure (product description, serial number, and other appropriate identification);
- b) detailed description of the animal model used, the rationale and justification for its use. The pre-procedural assessment of each animal shall include documentation of health status as well as gender, weight, and age of the animal;
- c) description of the implantation procedure, including delivery, deployment, sizing technique, device anatomic location, imaging technique(s) and any procedural difficulties;
- d) description of the pre-procedural and post-procedural clinical course of each animal including clinical observations, medication(s) and interventions used to treat serious adverse events. Describe anticoagulation or antiplatelet drug regimen used as well as therapeutic level monitoring methods, if applicable;
- e) any deviations from the protocol or amendments to the protocol and their significance;
- f) names of the investigators and their institutions along with information about the implanting personnel and the laboratory's experience with heart valve substitute and/or heart valve repair device implantation and animal care;
- g) interpretation of data and a recommendation relative to the expected clinical safety and effectiveness of the heart valve repair device system under investigation;
- h) for survival studies, the study pathology report shall include gross and radiographic examination and histopathology findings, including gross photographs of the device and surrounding tissue, for each explanted heart valve repair device;
- i) for survival studies, detailed full necropsy reports for each animal in the study that includes an assessment of the entire body including such findings as thromboembolism or any other adverse effects putatively from the heart valve repair device.

Further details of the test report depend on the defined test protocol.

7.4 Clinical Investigations

7.4.1 General

The requirements of ISO 14630 and ISO 14155 shall apply. Clinical investigations shall be performed for new or modified heart valve repair devices and expanded indications for use to investigate those risks and aspects of clinical performance that cannot be fully evaluated from pre-clinical or other available data. If a determination is made that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided.

Clinical investigations shall be designed to evaluate the heart valve repair device in its intended use. The studies shall include an assessment of adverse events related to risks arising from the use of the heart valve repair device and from the procedure. The clinical investigation shall include pre-procedure, peri-procedure, and follow-up data from a specified number of subjects, each with a follow-up appropriate for the device and its intended use. The clinical investigation programme shall be designed to provide

substantial evidence of acceptable performance, safety, and risk–benefit ratio to support the intended labelling of the device.

The phases of a clinical programme typically include a pilot phase (e.g. first-in-human or feasibility studies), a pivotal phase (studies to support market approval), and a post-market phase. Compassionate use is a separate process and is not considered part of the clinical programme. A series of patients receiving a novel device under compassionate use shall not be used as a substitute for any clinical investigational study. Prior to embarking on a pivotal clinical investigation, pilot phase studies shall be considered to provide initial information regarding clinical safety and effectiveness. A scientific justification shall be provided if pilot phase studies are not to be undertaken. The information derived from the pilot phase may be used to optimize device design prior to initiation of a larger clinical investigation following further pre-clinical testing.

A pivotal clinical investigation shall be designed to ensure:

- a) the presence of a well-defined, clinically relevant question;
- b) an acceptable level of risk-benefit for the patient considering the available alternatives and standard of care;
- c) an appropriate study design to answer the clinical question, including a well-defined patient population, study endpoints and duration.

A randomized study design for a pivotal trial should be considered based on the following:

- a) ethical considerations may require a head-to-head comparison with alternative treatments or standard of care;
- b) randomized trials provide the highest quality scientific evidence and minimize bias;
- c) randomized trial results may promote adoption of effective therapies;

For clinical investigations to serve as a basis for market approval there should be sufficient data to support safety and effectiveness and a favourable risk-benefit ratio. These studies should include specific inclusion/exclusion criteria, use of accepted endpoint definitions, have a rigorous way of collecting information on defined case report forms, a rigorous system to monitor the data collection, defined follow-up intervals, and complete follow-up of the study populations.

7.4.2 Study considerations

7.4.2.1 General

The decision to use a medical device in the context of a particular clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure in comparison with the risk and anticipated benefits of alternative procedures (ISO 14971). With valve replacement devices, haemodynamic performance and those adverse events which are directly valve-related can be measured and reasonably attributed to the device. Because valve repair devices modify the native valve and its function, haemodynamic and clinical performance including adverse events may be differentially affected by factors relating to the native valve itself as well as factors other than the device itself, including:

- a) patient comorbidities;
- b) the underlying pathological process and whether it continues to progress;
- c) pathology of the native tissue in the intended patient population (e.g. leaflet geometry and tissue material properties in degenerative mitral valve disease);
- d) the degree of haemodynamic improvement achieved;
- e) technical factors involved in implantation;

- f) appropriate selection of available sizes and/or shape configurations;
- g) the potential for adverse haemodynamic effect.

Imaging assessment is an essential aspect of the clinical investigation for patient selection, device placement, and patient follow-up. To ensure optimal anatomic evaluation, device position, and functional assessment, multiple imaging modalities (e.g. TEE, TTE, CT, MRI, fluoroscopy, PET) may enhance assessment and should be used where applicable (see also [Annex R](#)). The latest imaging guidelines from professional societies shall be followed in performing these imaging procedures. High quality images shall be ensured by use of quality control systems. An independent Core Lab (core laboratories) shall be used to carry out analysis and interpretation for pivotal studies. Clinical site training and certification shall be conducted before enrolment in collaboration with the independent Core Lab (See Reference [\[32\]](#)). Imaging follow-up time points shall be specified and justified, and should be complete at each specified time point.

The clinical investigation plan (CIP) shall clearly define the objectives of the study. The CIP shall specify safety and effectiveness endpoints (see [Annex S](#)), linked to study success criteria. The CIP shall specify study-related adverse events, including device and/or procedure-related adverse events in accordance with [Annex Q](#) and published definitions. The definitions of the outcome measures should be consistent with those employed in previous studies of heart valve repair devices, when appropriate. The study design shall include a pre-specified statistical analysis plan and success criteria (e.g. new devices should be non-inferior to standard of care).

The manufacturer is responsible for ensuring collection of appropriate information. The study design shall be consistent with the aims of the CIP. For a given study, the CIP and data collection forms should be standardized across institutions and investigators. Studies should employ measures to minimize bias. The use of an independent clinical events adjudication committee to classify events against pre-established criteria, and Core Lab are recommended for outcomes that might be prone to inter-observer variability.

Study monitoring shall be conducted in accordance with ISO 14155. To ensure patient safety, a safety monitoring plan shall be established. Study oversight shall be provided by an independent data safety monitoring board for evaluation of patient safety and CIP adherence; the monitoring board shall be empowered to make recommendations for or against study continuation.

Study designs may vary depending on the purposes of the assessment and/or the technology (novel technology versus modification to well-established device). Study populations shall be representative of the intended post-market patient population, including aetiology and pathology. Further, studies shall be designed to ensure collection of all CIP specified follow-up information in all subjects entered into the study unless subjects specifically withdraw consent for follow-up. In this case, follow-up in these subjects will end at the time of the withdrawal except that, depending on local legal requirements relevant to subject privacy, patients who withdraw consent may still be followed for survival.

As with all new devices implanted within the cardiovascular system, explant analysis is vital as part of clinical assessment. Valves and other devices explanted at subsequent surgical operations or at autopsy should be assessed by independent cardiovascular pathologists with results of analyses reported in accordance with the CIP including operative or autopsy photographs of the device *in situ* and after explantation.

Different considerations may apply for pilot phase studies:

- a) pilot phase studies are exploratory in nature and may not require pre-specified statistical hypotheses. Robust interpretation of the results and their generalizability is usually limited, due to the small number of subjects and participating clinical investigators;
- b) the consent process shall inform the subjects of the pilot phase nature of the study and alternative options;
- c) limitation on rate of enrolment (e.g. evaluation of acute outcomes after each patient and before treating the next patient);

- d) oversight of the study safety by a Clinical Events Committee (CEC) and/or Data Safety Monitoring Board (DSMB) with defined study continuation criteria;
- e) initial assessment of device safety and effectiveness;
- f) re-evaluation of risk / benefit ratio based upon study outcomes.

For modification of a marketed device, a clinical investigation shall be considered based on the risk analysis. Clinical investigations are recommended for design changes of a marketed device that may affect the safety and effectiveness (e.g. change in blood contacting materials, changes that alter the flow characteristics or haemodynamics, changes that affect the mechanical loading to the anatomy).

Important differences between surgically implanted and transcatheter devices need to be considered for study design.

7.4.2.2 Direct Visualization Surgical Devices

Annuloplasty rings or bands (complete and incomplete) have been used for more than four decades (e.g. mitral, tricuspid). They vary in their construction materials (rigid, semi-rigid or flexible), in their 3-dimensional shape and in their surfaces exposed to the blood stream and are usually available in a range of sizes. Biodegradable or absorbable annuloplasty devices are also available for paediatric use.

When used in degenerative disease processes causing primary regurgitation, annuloplasty rings and bands are usually combined with surgical repair or reconstruction of the leaflets and/or chordae so that the success of the procedure is determined primarily by the surgical techniques used, with the annuloplasty ring providing support for the repair in addition to reducing the size of the annulus. In these cases, haemodynamic evaluation of the device itself is impossible, although other aspects of its design and construction can be evaluated.

When used alone in secondary regurgitation of functional or ischaemic origin, the device itself has a greater influence on the haemodynamic outcome, although specific left ventricular pathology, surgical implantation technique and sizing issues can all have important effects and need to be taken into account in clinical investigations.

Other factors which need to be evaluated in new surgical annuloplasty devices are structural integrity over time and biocompatibility (in cases of new materials). Tissue erosion can lead to suture line disruption and loosening of the device, and excessive thrombogenicity can cause thromboembolism. Pannus formation can spread onto adjacent leaflets and compromise the repair. Long-term complete follow-up is necessary to detect susceptibility to these complications and to ensure that reduction in valvular regurgitation is maintained over time.

Surgical repair of atrioventricular valves that are regurgitant due to organic valvular or subvalvular defects (primary or organic valvular regurgitation) shall be regarded as the standard on which to base comparisons because a direct visual approach coupled with detailed echocardiographic assessment allows definition of and the best possibility of correction of the mechanism of regurgitation in the individual patient. For all types of atrioventricular valve regurgitation (i.e. organic and functional), reparative efforts should be undertaken with the aim of a complete 'cure' of the regurgitation, although this may not be possible in all cases.

7.4.2.3 Transcatheter Devices

Clinical evaluation of new transcatheter devices (indirect visualization) for valve repair carries many of the caveats mentioned above for surgical annuloplasty devices in that many technical and patient-related variables will influence outcome in addition to the device itself and will need to be accounted for in clinical investigations. For example, these devices may cause complications specific to their modes of access and device design (e.g. progressive mitral stenosis, coronary sinus perforation or thrombosis) or compromise future surgical treatment.

Immediate 'procedural success' in the correct deployment of the device without complications and some degree of reduction in regurgitation shall be followed with longer term evaluation to show that

the reduction is maintained over time, an improvement of ventricular function, and that the device is durable and does not cause thromboembolism or other design-specific complications. Completeness of follow-up is essential.

7.4.3 Study endpoints

The choice and timing of primary and secondary study endpoints shall be driven by the study objectives, the disease, the patient population, the technology, the post-operative treatment (e.g. heart failure medication, antithrombotic medication) and anticipated risks. In general, endpoints shall consider safety and effectiveness, time-related valve safety, quality of life, symptomatic and functional status, and device and procedural success. Other tertiary or descriptive endpoints should be considered relative to the technology. Further suggestions for clinical investigation endpoint selection and timing for valve repair devices are provided in [Annex S](#).

7.4.4 Ethical considerations

Although novel valve repair technology may have been extensively tested *in vitro*, by computer simulation and by implantation in animals, human studies are essential yet carry significant risk to patients, especially in pilot phase studies. Diseased human hearts are structurally and functionally different from healthy or diseased animal hearts. Further, the investigators who will implant the device will be subject to a learning curve. Even if similar devices have been previously implanted successfully, differences in route of access, deployment and/or fixation techniques could impose unforeseen hazards.

The choice of patients to receive the first implants of a novel technology places enormous responsibility on both manufacturers and investigators and raises important ethical issues. Choice of objective and skilled investigators who will implant the new device is equally important. Relevant guidance on conflict of interest has been provided by regulatory agencies and recommendations by The Institute of Medicine of the National Academies (See Reference [14], [26]). Manufacturers shall not offer financial incentives to the institution or investigators to implant the device. Compensation of patients for the costs for participating in the clinical investigation shall be limited to that appropriate based on national regulations and, in line with ISO 14155, shall not be so large as to encourage patients to participate.

See also [7.4.6](#) for additional detail for site and investigator selection considerations.

7.4.5 Distribution of subjects and investigators

Clinical investigations shall be conducted in institutions with appropriate facilities, case-load and case-mix and by investigators with appropriate experience, skills, and training. Emphasis should be placed on the multidisciplinary heart team approach (See references [33], [40], [41], [42]). Clinical investigations shall be designed to include enough subjects, investigators, and institutions to be representative of the intended patient and user populations to provide generalizable results. The design should include consideration of and justification for such aspects as disease aetiology, disease severity, gender, ethnicity, age (e.g. adult, paediatric) and other special patient populations as appropriate. The study shall be designed to ensure that patient enrolment is sufficient to accommodate a spread of clinical experience and exposure to the device while allowing a reasonable learning curve. Consideration and justification should also be made to account for any expected differences in standard of care or patient outcomes based upon the geographic distribution of the intended patient or user populations. The CIP shall specify and justify the planned number of institutions (including geographical distribution), the minimum and maximum number subjects to be included for each centre, the maximum number of investigators per institution, as well as the target patient population. Criteria relevant to the qualification of sites and clinical investigators include:

- a) sites:
 - 1) suitable distribution of sites;
 - 2) access to the defined patient population;
 - 3) presence of a local or central Institutional Review Board (IRB)/Ethics Committee (EC);

- 4) qualified centres, following the guidelines on operator and institutional requirements published jointly by the Society for Cardiovascular Angiography and Interventions (SCAI), the American Association for Thoracic Surgery (AATS), the American College of Cardiology (ACC) and the Society for Thoracic Surgeons (STS) (See Reference [6], [13], [40], [41]);
 - 5) involvement of a multi-disciplinary heart team in patient selection;
 - 6) expert imaging with accredited operators and facilities (see also [Annex R](#));
 - 7) appropriate study coordinator and other administrative staff associated with data collection or coordination of the study;
 - 8) adequate resources (e.g. facilities and equipment, security and storage, working space for monitor(s) and additional equipment);
 - 9) compliance with Good Clinical Practice (GCP), including but not limited to: regulatory agency and IRB/EC approval prior to study initiation; proper consenting of all research subjects; CIP adherence, with any deviation properly approved or documented; proper adverse event reporting; and adequate device accountability;
 - 10) experience with clinical investigations;
 - 11) acceptable outcomes of previous regulatory inspections.
- b) clinical investigators:
- 1) qualifications by education, training (by manufacturer or medical experts), relevant experience, and meeting all applicable regulatory requirements;
 - 2) motivation to continue patient recruitment and to undertake long term accurate follow-up;
 - 3) prior clinical research experience in the relevant area;
 - 4) enrolment history in previous related studies;
 - 5) avoidance of competing studies (e.g. to avoid selection, channelling biases);
 - 6) minimising potential conflict of interest. If there are substantial conflicts of interest with the manufacturer, such conflicts must be managed, which should involve (but not necessarily be limited to) consideration of the use of a non-conflicted physician for patient recruitment, informed consent, and reporting (See references [14], [26]).

7.4.6 Statistical considerations including sample size and duration

The manufacturer is responsible for selecting and justifying the specific statistical methodology used. The size, scope, and design of the clinical investigation shall be based on:

- a) the intended use of the device;
- b) the results of the risk analysis;
- c) measures that will be evaluated;
- d) the expected clinical outcomes.

A randomized controlled trial, assessing superiority or non-inferiority as appropriate, should be considered to minimize bias when existing objective performance and safety metrics are inadequate. Depending on the scope and objectives of the clinical investigation, other designs may be appropriate.

The decision to use a medical device in the context of a particular clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure in comparison with the risk and anticipated benefits of alternative procedures (ISO 14971). If a comparable device is on the market, the study control may be the comparable device or another active comparator, such as surgery.

or medical therapy. If a comparable device is not on the market, randomization against an appropriate active comparator should be used. If the study uses a non-inferiority design, the non-inferiority margin should be justified and, to the extent feasible, based on prior data from comparable devices.

For pivotal studies (single-arm or concurrent control), the sample size shall be justified and shall be sufficient to enable assessment of the study safety and effectiveness endpoints of the heart valve repair device in the intended population. Standard statistical methods shall be used to calculate the minimum sample size with prior specification of a 5 % Type 1 error rate (one-sided). The statistical power, confidence intervals and effect sizes to be detected shall also be specified. Sample size considerations shall take into account the standard of care and available safety and effectiveness data (including post-market or published data) on relevant therapies with similar intended use.

For a new heart valve repair device, in a population with acceptable surgical risk, the sample size shall include a minimum number of 150 patients receiving the subject device for each indicated valve location, each of whom is intended to be studied for at least 1 year (understanding that death occurring prior to 1 year is captured and included in the 1-year follow-up analysis). In addition, at least 400-patient years of data are required in the pre-market setting to assess late adverse events (e.g. thromboembolism, device thrombosis, haemorrhage, infective endocarditis). The 400 patient-years criterion can be met by further pre-market follow-up of the 150 patients beyond 1-year or by enrolment of additional patients. This aligns with sample size requirements for surgical valve replacement devices (see ISO 5840-2:2015).

If the population to be studied is not of acceptable risk to allow surgery to be undertaken, a smaller sample size may be justified based on a robust statistical analysis which takes into consideration the anticipated risk benefit profile. The approved indication for use shall be consistent with evidence gained from the patients studied. Departures from the recommended 400-patient year sample size shall be adequately justified. [Table 5](#) below provides a range of sample sizes that will exclude an adverse event rate that is double the expected rate.

Table 5 — Patient-years required to exclude a linearized event rate that is double the expected rate with 80 % power

Expected Adverse Event Rate (% per year)	Adverse Event Rate to exclude (null hypothesis, H ₀), % per year	Patient-years
1,0	2,0	972
2,0	4,0	486
2,4 *	4,8	400
3,0	6,0	324
4,0	8,0	243
5,0	10,0	194
6,0	12,0	162
7,0	14,0	139
8,0	16,0	122
9,0	18,0	108
10,0	20,0	97

The recommendation to collect 400-patient years of data is based upon the following considerations: Using a null hypothesis that the actual adverse event rate is twice the event rate currently accepted for similar devices (See Reference [\[20\]](#)), with probabilities of one-sided type one error of 5 % and probability of type 2 error 20 % (power = 80 %), the sample size (in patient-years) is determined to be $9,72/CR$, where CR is the complication rate currently considered acceptable for similar devices. For example, to detect a CR of 2,4 %/year or higher, this would require $9,72/0,024 = 400$ patient-years (See Reference [\[21\]](#)).

In addition to the requirements established above, the CIP shall specify the total duration of the study, including long-term patient follow-up which may continue in the post-market setting (see also [7.4.10](#)). The study duration shall be established based on the specific purposes of the study as identified by the

risk assessment, the intended application, the outcomes measured, and, if relevant, the type of device modification. The intended application includes the disease and population for which the device is intended, including the expected duration of survival in such a population without the device at issue and survival in patients treated with an available active comparator.

7.4.7 Patient selection criteria

The inclusion and exclusion criteria for patient selection shall be clearly defined. The intended patient population shall be specified and any salient differences between the intended population and those studied shall be justified. The study should only include subjects who are willing and able to participate in the follow-up requirements.

The following aspects should be taken into consideration when developing inclusion and exclusion criteria to ensure that the expected benefit of treatment outweighs the risk to subjects:

- a) patient demographics (e.g. age, gender, ethnicity);
- b) disease aetiology (e.g. stenosis, primary or secondary regurgitation);
- c) severity of valve disease;
- d) symptomatic versus asymptomatic patients;
- e) predicted risk of surgical morbidity or mortality (e.g. STS Score^[13], logEuroSCORE^[31]);
- f) co-morbid conditions (e.g. myocardial infarction, other valve disease, coronary or peripheral artery disease, atrial septal defect, patent foramen ovale, infective endocarditis, rheumatic heart disease, degenerative neurological disorders, frailty, previous cardiac interventions, prior stroke or systemic embolism, chronic kidney disease, hematologic disorders, chronic lung disease);
- g) ventricular function and chamber size (e.g. ejection fraction, systolic/diastolic dimension or volumes);
- h) haemodynamic stability (e.g. mechanical circulatory assist devices, inotropic support);
- i) surgical status (e.g. elective, urgent, emergent, salvage);
- j) tolerance for procedural/post-procedural anticoagulation or antiplatelet regimens;
- k) life expectancy;
- l) device/procedure specific anatomical considerations (e.g. valve size, calcification, congenital abnormalities, access site conditions, device placement location, ability to tolerate TEE);
- m) access to sufficient follow up treatment (all types of physical and medicinal therapy).

7.4.8 Clinical data requirements

7.4.8.1 General

Clinical data, including adverse events, shall be recorded for all subjects in the study as required by ISO 14155. Consideration and appropriate justification should be made for the collection and analysis of site reported versus Core Lab adjudicated data.

The CIP shall include an explant pathology protocol with detailed instructions for evaluation by an independent cardiac pathologist (including operative or autopsy photographs) and instructions for the return of the explanted device to the manufacturer, where appropriate. Whenever feasible, the explanted device shall be subjected to appropriate functional, imaging and histopathological investigations. In the event of subject death, valuable information about implanted devices can be obtained by autopsy which should be encouraged whenever possible.

If any of the above data are deemed not applicable, a justification shall be provided.

7.4.8.2 Baseline

The following data shall be collected:

- a) demographics (e.g. age, gender, ethnicity);
- b) baseline information (e.g. weight, height, blood pressure);
- c) co-morbidities (e.g. liver, kidney and lung disease, substance abuse, smoking history, diabetes, hypertension, hypercholesterolemia);
- d) cardiovascular diagnosis (e.g. valvular lesion and aetiology) and co-existing cardiovascular diseases (e.g. heart failure, cardiomyopathy, aneurysm, cerebral vascular disease, peripheral vascular disease, coronary artery disease, history of endocarditis, history of thromboembolism, previous myocardial infarction), and cardiac rhythm;
- e) New York Heart Association (NYHA) functional class and relevant Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score or logistic European System for Cardiac Operative Risk Evaluation (logEuroSCORE), or both (STS score is recommended for all subjects). Frailty and quality of life indicators and/or exercise tolerance tests should also be considered (see references [13], [31], [33], [42], [43]);
- f) previous relevant interventions (e.g. coronary artery bypass, coronary artery angioplasty, percutaneous valvuloplasty [position], operative valvuloplasty [position], valve repair [position], previous heart valve implantation [position], peripheral vascular interventions);
- g) echocardiographic and other relevant imaging data to provide cardiac haemodynamic, geometric, and functional information (e.g. ventricular function), to characterize the diseased valve and to assess implant site and annulus size;
- h) relevant imaging data for assessment of potential deployment approach;
- i) haematological studies assessing hepatic, cardiac and renal status, and including haematological / coagulation profile.

If any of the above data are deemed not applicable, a justification shall be provided.

7.4.8.3 Peri-Procedure Data

The following data shall be collected:

- a) name of operator(s);
- b) utilization time (e.g. procedure room entry/exit time, access site entry/exit time, length of hospital stay);
- c) date/time of procedure;
- d) type of procedure suite (e.g. operating room, hybrid room, cardiac catheterization laboratory);
- e) methods of anaesthesia (e.g. general, local, conscious sedation);
- f) medications, including start/stop, dosage, changes, change justification (e.g. antithrombotic regimen, inotropes);
- g) list of all procedural devices (e.g. guidewires, catheters, introducers);
- h) list of monitoring devices (e.g. arterial line, pulmonary artery catheter, pulse oximetry);

- i) mechanical circulatory assist devices (pre, intra, post-procedural), and associated parameters (e.g. activated clotting time, core body temperature, cardiopulmonary bypass time, inotropic support, cardiac arrest time);
- j) imaging modalities (e.g. fluoroscopy, TEE, TTE, CT);
- k) any changes from original diagnosis;
- l) heart valve repair device (e.g. type, models, sizes, device identifier), implantable ancillary devices or accessories;
- m) any concomitant interventions or procedures;
- n) elements of procedure, including any adjunctive procedures performed (e.g. contrast volume, radiation dosage (see Reference [35]), embolic protection, rapid pacing);
- o) access site and technique (e.g. sternotomy, thoracotomy, transfemoral, transapical);
- p) assessment of implant site and annulus size, or other relevant sizing measure of patient;
- q) precise anatomical implant position in relation to leaflets, tissue annulus;
- r) assessment of handling, visualization, deployment, orientation, implant location and insertion/withdrawal of delivery system, where appropriate;
- s) procedural complications, including acute interventions (e.g. conversion to surgery);
- t) quantitative and qualitative evaluation of deployed device by echocardiography and/or other relevant imaging and haemodynamic modalities, as defined in the CIP. At a minimum, pressure gradient and degree of regurgitation should be documented.

If any of the above data are deemed not applicable, a justification shall be provided.

7.4.8.4 Follow-Up Data

Follow-up data shall be collected at 30 days, at least one specific time point between 3 and 6 months, at one year, and at a minimum annually thereafter until the investigation is completed, as defined in the CIP. Physical examination of patients is recommended. The following evaluations should be performed at all follow-up assessments unless an adequate risk analysis justifies a less frequent interval. Depending on the investigational design, additional data collection times might be appropriate.

The following data shall be collected:

- a) date, type (in person, telephone), location and type of health care professional performing follow-up (e.g. investigator, primary care physician, nurse);
- b) results of physical examination;
- c) New York Heart Association functional class (see Reference [43]);
- d) health-related quality of life indicator(s);
- e) functional assessment (e.g. 6 Minute Walk Test [43], peak VO₂);
- f) device assessment (e.g. implant location, geometry, structural integrity, orientation);
- g) haemodynamic evaluation by Doppler echocardiography, or other relevant methodology (the methodology chosen should be consistent for consecutive studies, see Annex R);
- h) heart rate, rhythm and conduction abnormalities;
- i) tests for haemolysis (e.g. plasma free haemoglobin), if clinically indicated. Other blood tests may be indicated;