INTERNATIONAL STANDARD

ISO 5910

First edition
2018-06

Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

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

Reference number
ISO 5910:2018(E)

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

Published in Switzerland

Contents

Page

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

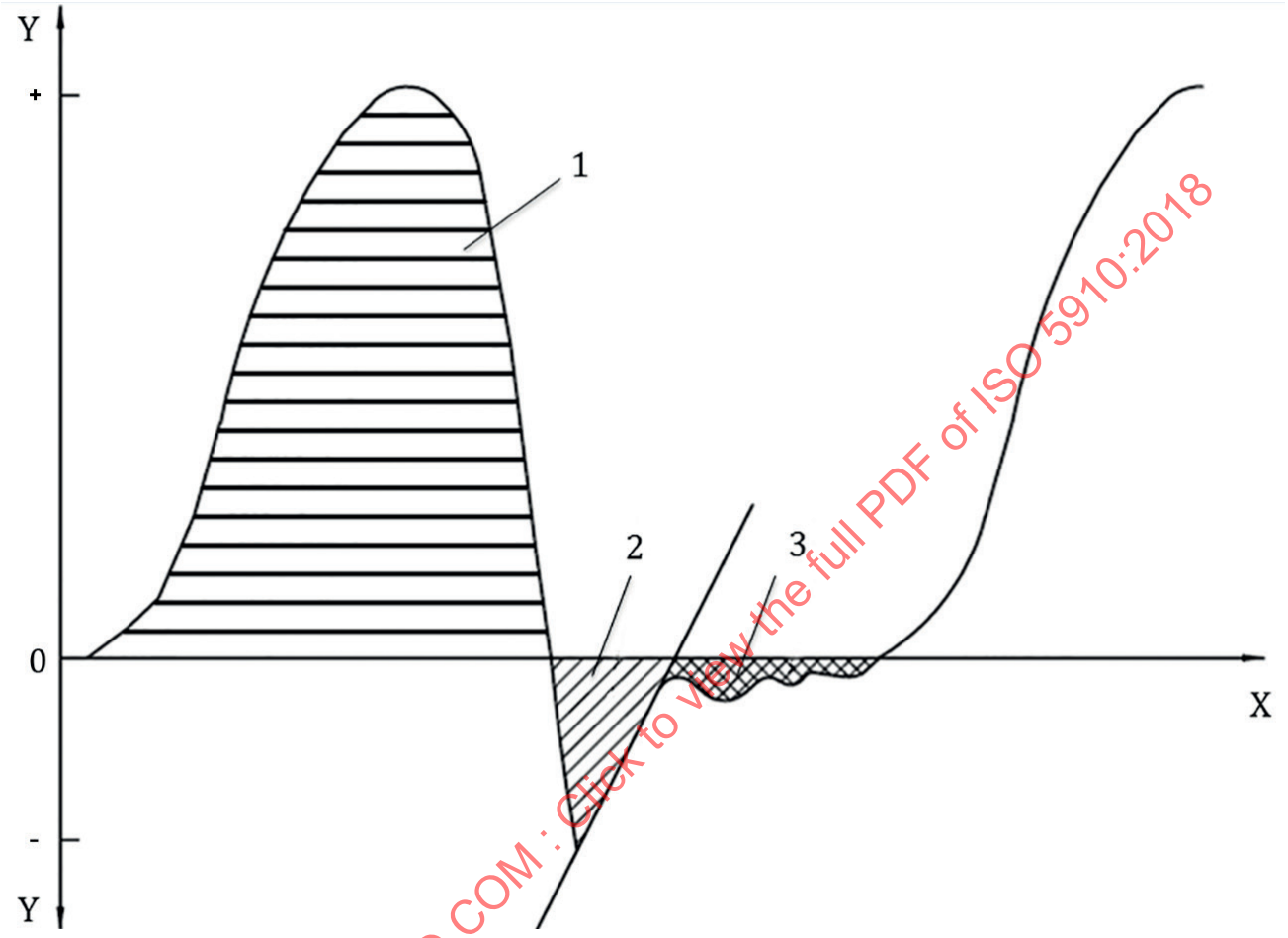
Note 1 to entry: This can be calculated as the square root of product of the weight in kg times the height in cm divided by 3 600. See Reference [30].

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 (cm^2);
$q_{v_{RMS}}$	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/cm^3).

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;

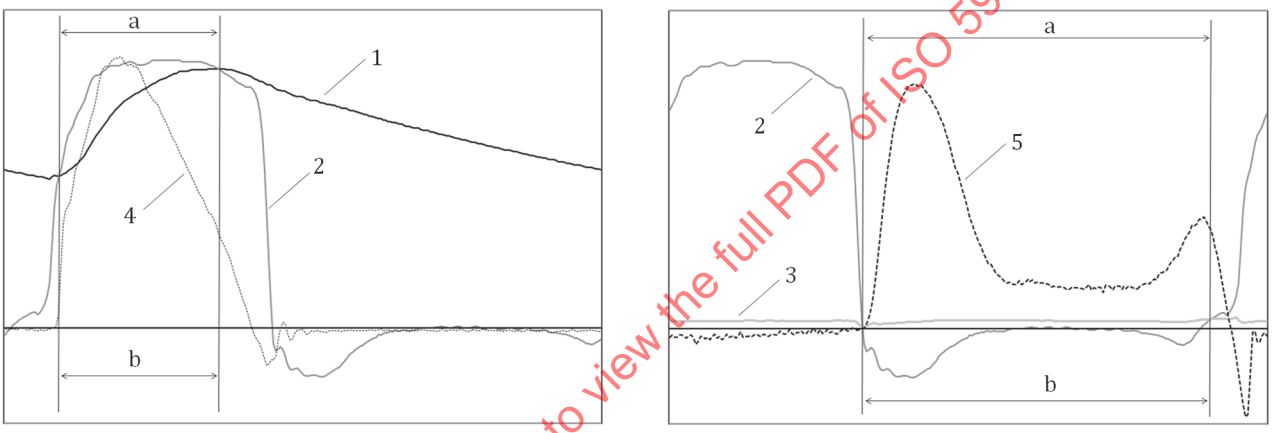
$q_v(t)$ is the instantaneous flow at time t;

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.

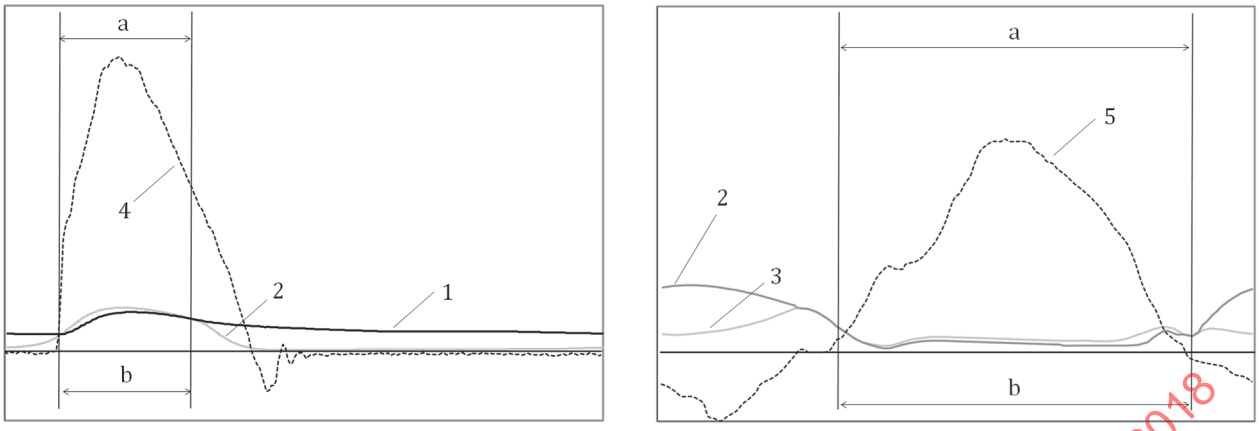
Note 4 to entry: See Figure 2 for representative aortic and mitral flow and pressure waveforms from *in vitro* testing. See Figure 3 for representative pulmonary and tricuspid flow and pressure waveforms from *in vitro* testing.



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 $q_{v_{RMS}}$ 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 ≈ Aortic end diastolic pressure + ½(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 ≈ Pulmonary artery end diastolic pressure + ½(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:

a) the ability to repair valve function;

b) the ability to resist migration and embolisation;

c) the ability to minimize haemolysis;

d) the ability to minimize thrombus formation;

e) biocompatibility;

f) the ability to resist corrosion;

g) 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:

a) purpose, scope and rationale for the test;

b) identification and description of the heart valve repair system elements tested (e.g. batch number, size, configuration);

c) identification, description and rationale for selection of the reference device(s) where appropriate;

d) number of samples tested and rationale for sample size;

e) detailed description of the test method including preconditioning to simulate clinical use;

f) pre-specified acceptance criteria, if applicable;

g) verification that appropriate quality assurance standards have been met (e.g. Good Laboratory Practice, ISO 17025);

h) deviations, if any, and discussions of the effect of the deviations on the scientific validity of the test results;

i) 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, H0), % 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 VO_2);

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;

j) status and duration of anticoagulant and/or antiplatelet therapy (e.g. International Normalized Ratio (INR) history);

k) cardiovascular medications (e.g. heart failure and antiarrhythmic medications) including start/stop dates, dosage, changes, change justification. It is recommended that this information also be collected on other medications;

l) adverse events as specified in Annex Q;

m) concomitant therapies, (e.g. cardiac assist, need for pacing);

n) complete operative report for reoperations or conversion to surgery;

o) date and cause of death;

p) explant analysis and autopsy report, if performed.

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

7.4.9 Clinical investigation analysis and reporting

The Clinical Investigation Report shall comply with ISO 14155. The Clinical Investigation Report shall include information on all subjects for whom implantation was planned (the "intent-to-treat" population). For randomized studies, the groups shall include all randomized subjects, even those who did not receive the implant. Additional analyses shall be performed on the subjects who actually received the implant (see also Annexes Q, R and S). Justification shall be provided for those who were randomized to but did not receive an implant.

Clinical investigations shall be registered on applicable clinical trial websites upon initiation, with subsequent outcomes reported, including disclosure of both positive and negative results. For both pre- and post-market studies, the following principles shall be followed:

a) reports shall state the percentage of follow-up completeness, the reasons for patients lost to follow-up, and provide the total number of patient follow-up years to permit linearized rate calculations for adverse events;

b) if investigations have been conducted during follow-up (e.g. echocardiography), the percentage of patients receiving the investigation and how they were selected shall be stated;

c) efforts shall be made to ascertain the cause of death, including contact with local physicians if the patient died elsewhere, obtaining details of any investigations performed shortly before death, and autopsy data and explant data if available. Reliance on national healthcare databases to simply record that death has occurred is insufficient. A high percentage of patients with unknown cause of death raises suspicion of device-related deaths.

7.4.10 Post-market clinical follow-up

Prolonged post-market follow-up is essential to capture long-term data on less common or unanticipated adverse events, on adverse events which are time-related (e.g. structural deterioration, adverse effects on native valve anatomy) and on long-term performance. The initial cohort of patients included in pre-market clinical investigations shall continue to be followed in the post-market setting. These patients are the best source of valid long-term data because they will have been extensively studied in the pre- and peri-operative periods with full documentation, and because overall mortality and adverse event rates can be calculated. Reasons for removing individual patients from longer-term follow-up shall be documented. To facilitate prolonged follow-up and avoid the need for re-consenting patients, informed consent that includes details regarding the planned duration of follow-up in the post-market period should be obtained at the time of initial clinical investigation consent.

Post-implant follow-up of the pivotal phase cohort shall be conducted in accordance with 7.4.8.4 of this document for at least 5 years.

Further follow-up to 10 years post implant shall be conducted on the pivotal phase cohort with endpoints designed based upon risk assessment and device claims. The 10-year post-implant study should collect safety and effectiveness data (e.g. death, cause of death, stroke, thromboembolism, quality of life, valve reintervention). In certain situations, 10-year follow-up might not be feasible (e.g. high-risk patients, elderly) and the follow-up duration shall be justified.

Beyond the initial pivotal phase cohort of patients, it may be appropriate to obtain clinical data from additional users and patients representative of the real-world clinical setting. This shall be performed with patients enrolled prospectively in a post-market clinical follow-up (PMCF) study and a methodology employed to minimize bias in patient selection.

The pre-market and post-market cohorts shall be analysed and reported separately and in aggregate.

Follow-up should be as complete as possible, avoiding self-reporting, include a clear statement of follow-up years in all reports to allow calculation of adverse event rates, and generate scientifically valid high quality data (i.e. reliable and robust) that is capable of generating the relevant evidence needed for informed clinical and regulatory decision making. If data from individual registries are to be relied upon for post-market follow-up, there should be independent verification that all consecutive patients are entered and that all receive the same type of follow-up. Registries should also have safety alert mechanisms in place to permit regular review of the data.

The principles of long-term post-market follow-up apply to the pre-market patient cohort, any additional patients enrolled within a PMCF study, and to patients in registries:

a) a common CIP shall be implemented to ensure accurate and complete long-term follow-up which is crucial in identifying all adverse events and the performance or effectiveness of the device;

b) follow-up shall occur prospectively at regular pre-specified intervals on a face-to-face basis wherever possible, preferably with an independent physician, rather than telephone contact or postal or email questionnaire;

c) follow-up should include physician examination of the patient wherever possible and any relevant investigations and imaging. The percentage of each follow-up method shall be reported. Retrospective data collection, especially after a long interval, has been shown to underestimate adverse event rates.

Annex A
(informative)

Rationale for the provisions of this document

A.1 Rationale for risk based approach

The rationale for basing this document on risk management is that the traditional requirements-based model cannot keep up with the speed of technological innovation. With the requirements-based model, manufacturers spend their time looking for ways to comply with the requirements of this document, rather than on developing new technologies that could lead to inherently safer products. The risk-based model challenges the manufacturer to continually evaluate known and theoretical risks of the device, to develop the most appropriate methods for reducing the risks of the device, and to implement the appropriate test and analysis methods to demonstrate that the risks have been reduced.

This document combines a requirement for implementing the risk-based model with a listing of best practice methods for verification testing appropriate to heart valve repair device evaluation. The intent of the risk assessment is to identify the hazards along with the corresponding failure modes and causes to identify the requisite testing and analysis necessary to evaluate the risk associated with each specific hazard. See Annex G for additional details related to this risk-based approach. The brainstorming/decision making/documentation process inherent in risk management provides the opportunity for the manufacturer to evaluate the best practice methods included within this document. The manufacturer may choose to follow the best practice method as defined within this document, or may deviate from the method and provide a scientific justification for doing so. The risk management file required by ISO 14971 should document these decisions, with rationale.

The risk-based model requires a collaborative environment between the device developer (the manufacturer) and the body responsible for verifying compliance with the applicable regulation regarding safety and effectiveness of the device. The manufacturer should strive for continuous improvement in device design as well as test methodologies that can ensure safety and effectiveness of a device under variable operational environments, with less reliance on years of patient experience for evidence of performance or effectiveness.

A.2 Rationale for preclinical *in vivo* evaluation

The overall objective of preclinical *in vivo* evaluation is to test the safety and effectiveness of the heart valve repair device in a biological environment with the closest practically feasible similarity to human conditions.

The preclinical *in vivo* evaluation is the final investigational step prior to human implantation. Therefore, it should provide the regulatory body with an appropriate level of assurance that the heart valve repair device will perform safely.

No single uniformly acceptable animal model has been established. Therefore, the animal model(s) selected should be properly justified in order to ensure the highest degree of human compatible conditions for the heart valve repair system pertinent to the issues being investigated. Since chronic studies are conducted to elucidate heart valve repair device functional performance, biological responses, structural integrity, and delivery system and valve-related pathology in a specific anatomical position, it is preferable to undertake this longer-term testing of the device in anatomical positions for which it is intended. Modifications to the anatomical structures in the preclinical *in vivo* animal model may be necessary based on how the heart valve repair device configures to the surrounding anatomy and repairs the functioning of the heart valve post-implantation.

The concurrent implantation of an active comparator device enhances the comparative assessment by providing a bridge to known clinical performance. In addition, such an approach facilitates the distinction between the complications related to the active comparator device versus those of the heart valve repair device under test.

A.3 Rationale for design verification and design validation testing

Verification and validation testing includes materials testing, preclinical bench testing, preclinical *in vivo* evaluation, and clinical investigations. Although clinical investigations are usually considered to be part of design validation, some of the requirements established under design input might be verifiable only under clinical conditions. The tests specified herein do not purport to comprise a complete test programme; a comprehensive test programme for the heart valve repair device should be defined as part of the risk assessment activities. Where the manufacturer's risk assessment concludes that the safety and effectiveness will be better demonstrated by other tests or by modifying the test methods included in this Standard, the manufacturer should include in the risk assessment a justification of the equivalence or superiority of the alternative test or test method.

The manufacturer should validate the design of the heart valve repair device, its packaging, labelling and accessories. For a new heart valve repair device, design validation typically occurs in two phases. In the first phase, the manufacturer reviews the results of all verification testing and the manufacturing process validations deemed critical to safety prior to the first human implant. The review can also include analysis of the scientific literature, opinions of clinicians and other experts who will be using the device and comparisons to historical evidence from similar designs. The output of the review should be that the device is safe and suitable for human clinical investigations. The second phase of design validation occurs in conjunction with the outcomes of the pre-market clinical investigation. The data from the approval phase clinical investigation should be reviewed to ensure that the device, its packaging, labelling and accessories are safe and suitable for their intended use and ready for market approval. These validation activities should be documented.

For a modification to an existing heart valve repair device design or manufacturing method, the concepts of verification and validation continue to be applicable but might be limited in scope. The risk analysis should define the scope of the verification and validation.

The use of clinical grade materials and components, as opposed to generic test samples, is important since fillers, additives, and processing aids can have profound implications on material properties. Testing should be designed to evaluate areas where materials are joined (e.g. welded, sutured, or glued) since these are potential areas for failure.

A.4 Rationale for imaging assessment

Echocardiography and Doppler echocardiography are presently accepted as practical and available methods for evaluating human cardiac function and the function of heart valve repair devices. Other imaging modalities (such as fluoroscopy, CT, and cardiac MRI) are complementary to echocardiographic assessment. The accuracy of these diagnostic procedures depends upon the skill of the operator. Therefore, all investigating institutions involved in the clinical evaluation of a specific heart valve repair device should employ the same imaging protocol and quality assessment (see Annex R).

A.5 Rationale for clinical evaluation reporting

Recommendations for reporting endpoints are contained within several publications (See references [22], [25], [38], [39]). The purpose of these guidelines is to facilitate the analysis and reporting of results of procedures on diseased cardiac valves. The definitions and recommendations are designed to facilitate comparisons among different clinicians, cohorts, delivery techniques and devices. A heart valve repair device undergoing clinical evaluation should function as intended, with valve complication rates within broadly acceptable performance criteria limits, based on published follow-up studies or based on the control group active comparator. To enable appropriate risk assessment, preoperative, peri-operative and follow-up data should be collated, analysed and reported.

The clinical evaluation of a heart valve repair device after implantation requires documentation of specified complications (see Annex S). A new or modified heart valve repair device should perform as well as existing heart valve repair devices. Where appropriate, randomized clinical trials should be conducted comparing the heart valve repair device against surgically implanted heart valve substitutes, heart valve repair procedures, substitutes or medical therapy. The clinical evaluation also requires formal statistical evaluation of the clinical data rather than descriptive statistics. Unanticipated valve-related complications will be reported and evaluated prior to the completion of the formal methods of overall performance evaluation. Statistical evaluation methods and assessment criteria of clinical data could be different between the populations studied, including paediatric and adult study populations. Given the perceived significant risks associated with heart valve repair devices and the unknown durability of such devices, post-market surveillance protocols should be established.

A.6 Rationale for device configuration within labelling and instructions for use

Sizing may be a relevant parameter for some heart valve repair devices, while some repair devices may be configurable in the anatomical location in some way beyond just size designations. The manufacturer should provide clear instructions (along with special handling conditions, warnings, and/or precautions) on how to configure the repair device in the intended anatomical location, to ensure optimal device functionality. Any changes that may occur in the sizing or configuration of the repair device or the surrounding anatomy after implantation should be presented in the instructions for use.

A.7 Rationale for human factors engineering

There is a published human factors standard, IEC 62366-1. Manufacturers should incorporate human factors engineering into their overall product development process to ensure the design and development of safe, effective, and easy-to-use heart valve repair devices. Human factor aspects that may result in errors during implantation of the heart valve repair device should be presented in the warnings and/or precautions in the labelling.

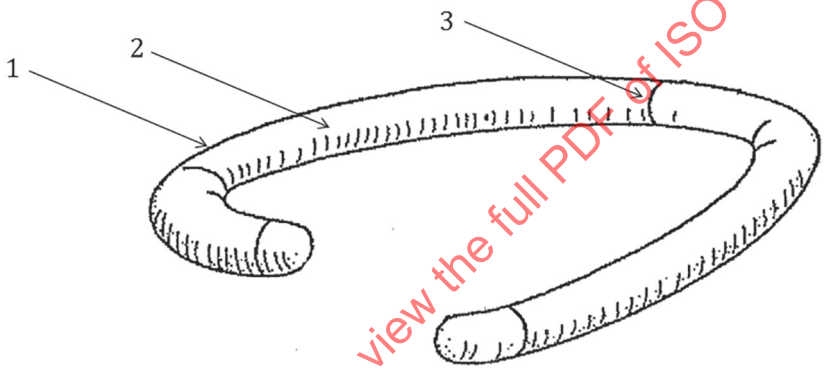
Annex B
(informative)

Examples of heart valve repair devices and delivery systems

B.1 General

This annex provides examples of heart valve repair devices and delivery systems that are intended to improve heart valve function. Refer to Clause 1 for the scope of this document.

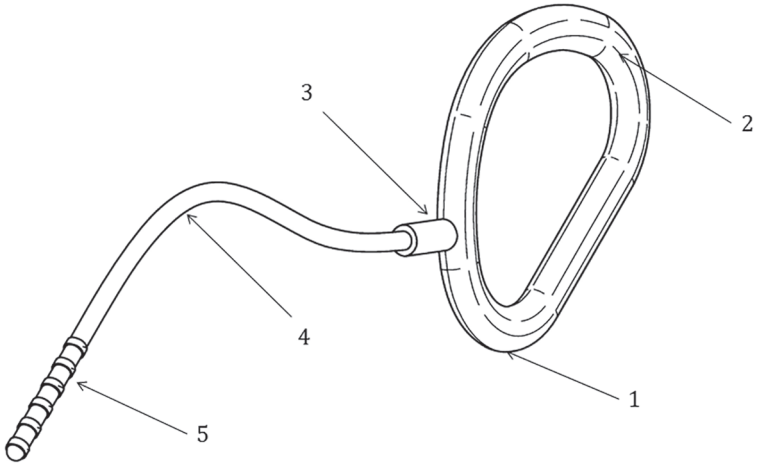
B.2 Examples of heart valve repair devices



Key

1 covering
2 stiffening element
3 suturing markers

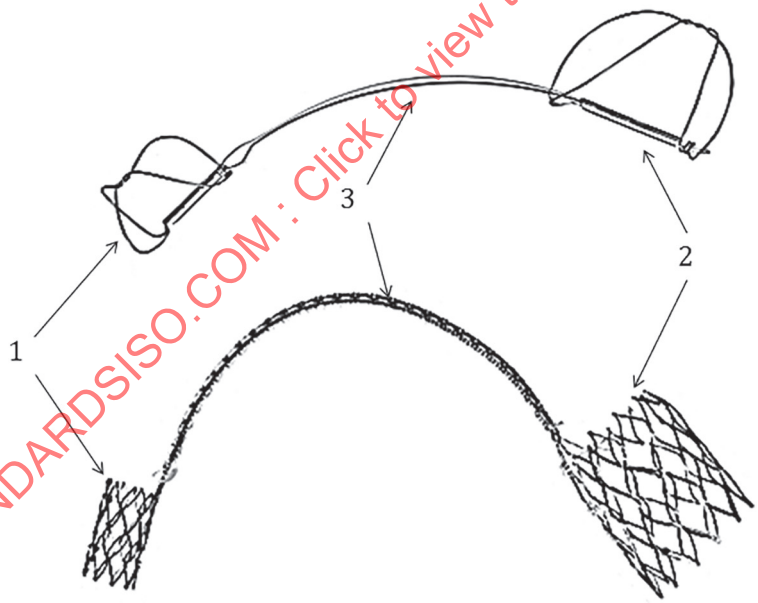
Figure B.1 — Example A: Surgical annuloplasty device



Key

1 covering
2 adjustable stiffening element
3 connector to annuloplasty ring
4 adjustment activation cable
5 connector to adjustment system

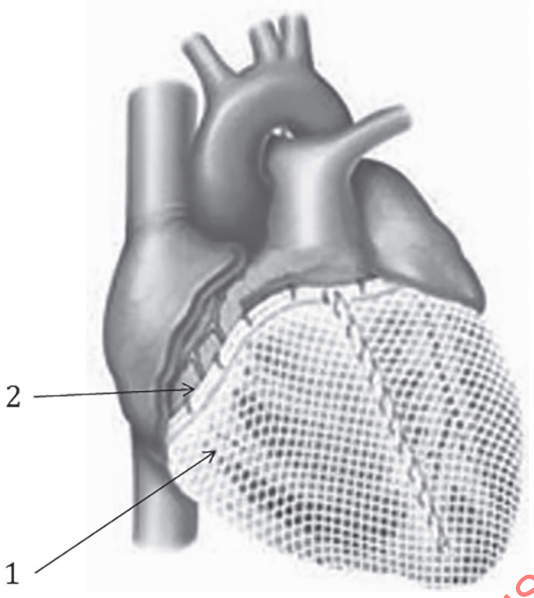
Figure B.2 — Example B: Adjustable annuloplasty device



Key

1 distal anchor
2 proximal anchor
3 bridging segment

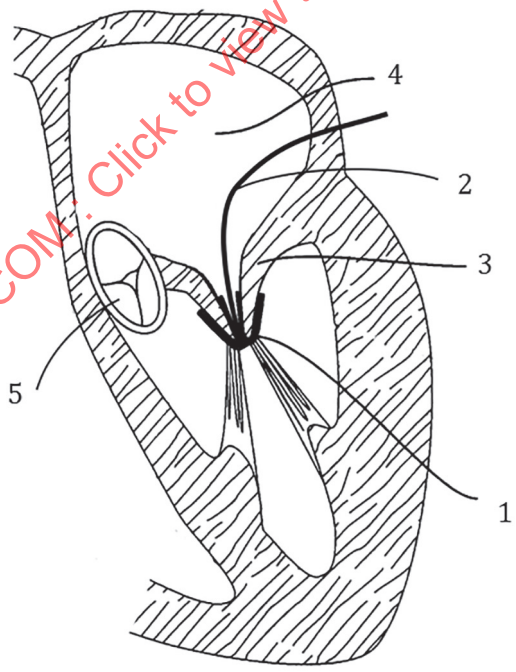
Figure B.3 — Example C: Coronary sinus reshaping devices



Key

1 compliant external mesh
2 mesh anchors/attachment

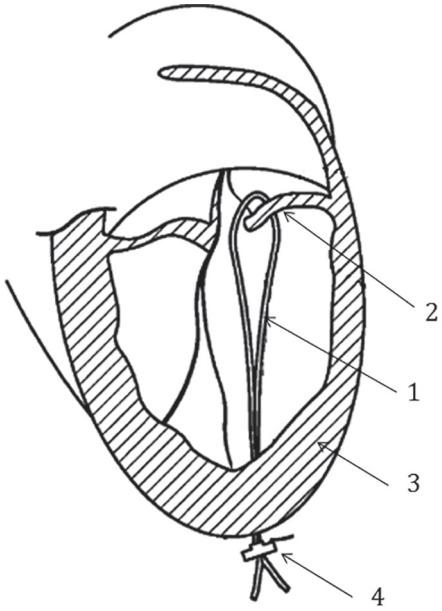
Figure B.4 — Example D: Ventricular reshaping device intended to improve valve function



Key

1 leaflet grasping arms
2 device attachment to delivery system
3 native mitral valve leaflets
4 left atrium
5 aortic valve

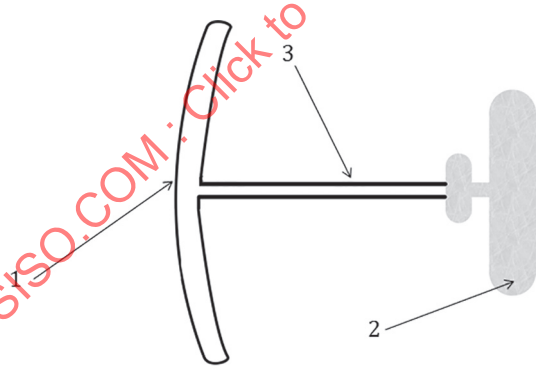
Figure B.5 — Example E: Leaflet clipping device



Key

1 synthetic chord
2 valve leaflet
3 ventricular wall
4 chordal attachment to ventricle

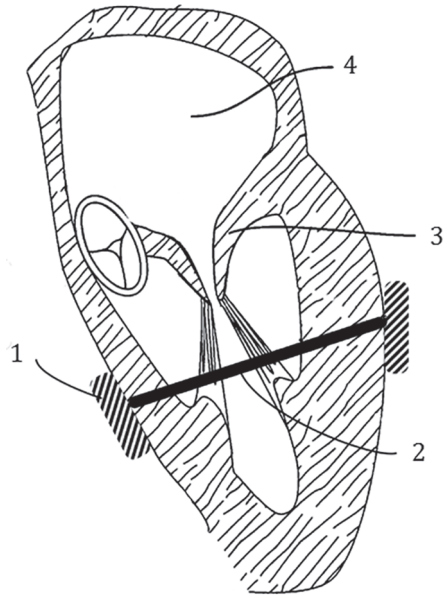
Figure B.6 — Example F: Artificial chordae device implanted percutaneously



Key

1 coronary sinus anchor
2 septal anchor
3 bridging segment

Figure B.7 — Example G: Septal shortening device

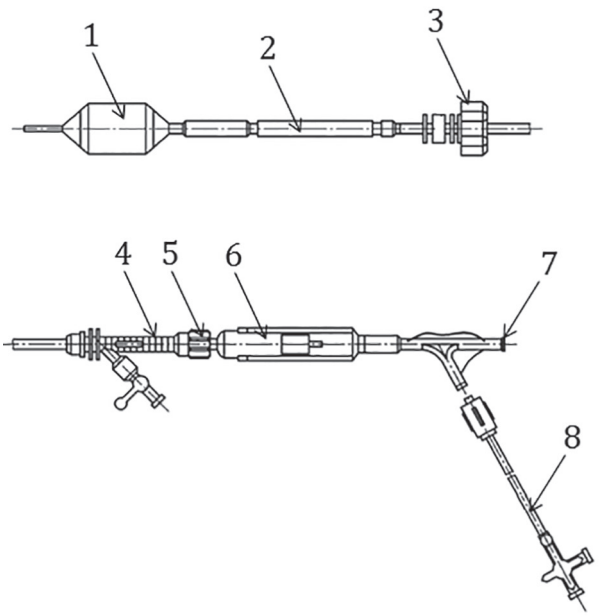


Key

1 ventricular pad
2 bridging element
3 mitral valve leaflets
4 left atrium

Figure B.8 — Example H: Ventricular reshaping device intended to improve valve function

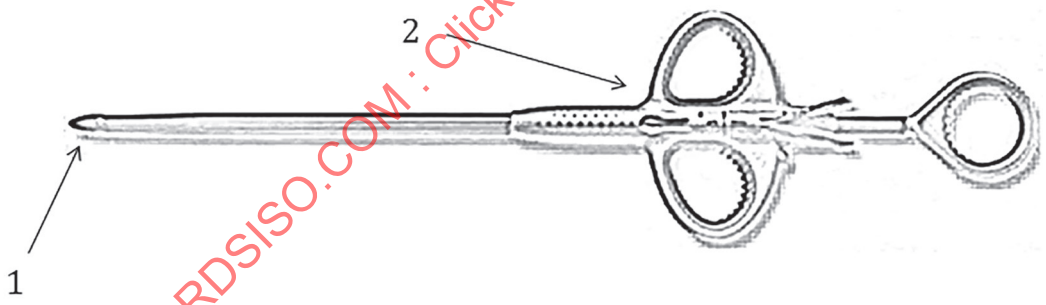
B.3 Examples of heart valve repair device delivery systems



Key

1	deployment balloon	5	outer sheath seal
2	introducer sheath	6	articulation level
3	introducer sheath valve	7	guidewire lumen
4	outer sheath	8	inflation port

Figure B.9 — Example I: Delivery system for balloon expandable heart valve repair device



Key

1 leaflet capturing jaws
2 operator handle

Figure B.10 — Example J: Delivery system for leaflet capturing device

Annex C
(normative)

Packaging

C.1 Requirements

The packaging requirements of ISO 11607-1 and –2 and of ISO 14630 shall apply.

C.2 Principle

Packaging shall be designed to ensure that the user is provided with a heart valve repair device, delivery system (if applicable), and accessories whose characteristics and performance are unaltered by normal transit or storage. Implants labelled "STERILE" shall be packaged so that they maintain their initial sterility assurance level under specified storage, transport and handling conditions, unless the package that maintains sterility is damaged or opened.

C.3 Containers

C.3.1 Unit container(s)

The heart valve repair device, delivery system (if applicable), and accessories shall be packaged in unit container(s) that meet the requirements of ISO 11607-1 and –2.

C.3.2 Outer container

The unit container(s) shall be packaged in an outer container(s) (sales/storage package) to protect the unit container(s).

Annex D
(normative)

Product labels, instructions for use, and training

D.1 Requirements

D.1.1 General

The labelling requirements of ISO 14630 and ISO 15223-1 and –2 shall apply.

Labels, instructions for use and training programmes shall be designed to ensure that the user is provided with information on handling, implanting or adjusting the heart valve repair device, and shall be approved and reviewed as part of the risk and quality management systems. Labels and instructions for use shall meet country-specific language requirements.

D.1.2 Unit-container label

Each unit container shall be marked with the following information:

— name or Trade Name;

— model number;

— serial/lot number;

— size/ configuration and device type, if applicable;

— the word “Sterile” or symbol if applicable and the method of sterilization;

— for sterile devices, the use by date or the expiration date;

— statement regarding single use only (if applicable);

— reference to see instructions for use for user information.

D.1.3 Outer-container label

Each outer container shall be marked with word(s), phrase(s) and/or symbol(s) for:

— name or Trade Name of device;

— name, address and phone number of manufacturer and/or distributor and other methods of contacting the manufacturer (e.g. facsimile number, email address). It may also be necessary to have the name and address of the importer and authorized representative of the manufacturer established within the importing country;

— model number;

— serial/lot number;

— size/ configuration and device type, if applicable;

— net contents;

— the word “sterile” or symbol and method of sterilization if applicable;

— for sterile devices, the use by date or the expiration date;

— statement regarding single use only (if applicable);

— devices intended for clinical investigations shall bear identification that the device is intended for investigational use only;

— any special storage or handling conditions as indicated in the device specification;

— warning against use of the device if the unit container has been opened or damaged;

— reference to see instructions for use for user information.

D.1.4 Instructions for use

Each heart valve repair device shall be accompanied by instructions for use that shall include at least:

— name or trade name of device;

— name, address and phone number of manufacturer and/or distributor and other methods of contacting the manufacturer (e.g. facsimile number, email address). It might also be necessary to include the name and address of the importer or an authorized representative of the manufacturer established within the importing country;

— revision level of IFU and implementation date;

— net contents;

— indications for use (the approved indications for use shall be fully consistent with evidence gained from the patients studied);

— any known contraindications;

— device description including available models and user required dimensions;

— description of any accessories required and reference to their instructions for their use;

— information on how the device is packaged/supplied;

— the word “sterile” or symbol and method of sterilization if applicable;

— statement that the device can or cannot be re-sterilized;

— statement regarding single use only (if applicable);

— devices intended for premarket clinical investigations shall bear identification that the device is intended for investigational use only;

— any special storage or handling conditions;

— warning against use of the device if the unit container has been opened or damaged;

— any warnings regarding handling, implanting or post-procedural adjustment of the device;

— any other warnings or precautions specific for the device (e.g. concomitant procedures, use with other devices, risk of radiation exposure due to fluoroscopy);

— instructions for resterilization (if applicable) including the maximum number of resterilization cycles, parameters which have been proven capable of achieving sterility of the device, and appropriate information relevant to other methods, apparatus, containers and packaging;

— specific instructions for device preparation (e.g. rinsing requirements for devices stored in chemical solution);

— specific instructions for implanting or using the device;

— specific instructions for sizing target implant site and selecting appropriate device size or configuration;

— list of potential complications;

— summary of clinical experience if required;

— the appropriate MR Safety designation (MR Conditional, MR Safe, or MR Unsafe) and a statement regarding MRI compatibility;

— post-procedure recommendations regarding patient follow-up and/or medication;

— any information or instructions which are intended to be communicated from the physician to the patient.

D.1.5 Labels for medical records

The manufacturer may provide peel-off, self-adhering labels, or equivalent, with each heart valve repair device that enables transfer of device information to the appropriate records. If provided, each label shall contain: the name or model designation, size/ configuration, and serial number of the heart valve repair device, and manufacturer identification, as applicable.

The size of the labels shall be sufficient to display the required information in a legible format. Excessive size shall be avoided. The number of required labels may vary based on individual country policies.

D.2 Training for physicians and support staff

If required by the risk assessment, the manufacturer shall establish a structured training programme for the physician and staff who will be involved in the peri-procedural care of the patient. The training programme shall be designed to provide the physician and staff with the information and experience necessary to control user-associated risks when the device is used in accordance with the instructions for use. Training records shall be maintained as evidence that physicians have received appropriate training.

The training programme shall include the following elements, where appropriate:

a) description of all system components, including the heart valve repair device and delivery system as well as a summary of the basic principles of operation;

b) complete review of the instructions for use including the indications for use, patient selection, contra-indications, precautions, warnings, potential adverse events, pre-procedure set-up, sizing the device, implant procedure, and post-procedure patient care;

c) review of imaging requirements for implanting the device such as fluoroscopy, CT, TTE, MRI and TEE;

d) hands-on bench top demonstration of the device and delivery system in a simulated model;

e) use of the device in a cadaver, or animal models or other appropriate models (e.g. robotic simulation system);

f) a clinical training programme, including proctored cases;

g) user verification/validation, determined by pre-defined criteria.

Annex E
(normative)

Sterilization

E.1 General

The sterilization requirements of ISO 14630 shall apply, together with the following.

For devices or accessories supplied sterile, sterilization shall occur by an appropriate method and shall be validated in accordance with internationally recognized criteria, as specified in ISO 17665-1, ISO/TS 17665-2, ISO/TS 17665-3, ISO 11135, ISO 11137-1, ISO 11137-2, ISO 11137-3, ISO 14160, and ISO 14937. If the manufacturer states that the heart valve repair device can be re-sterilized prior to implantation, adequate instructions in compliance to ISO 17664 shall be provided by the manufacturer, including validated parameters that have been proven capable of achieving sterility of the device.

For any reusable devices or accessories, the instructions for use shall contain information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging, and, where appropriate, the method of sterilization, and any restriction on the number of reuses.

Annex F
(informative)

Heart valve repair system characteristics

F.1 General

This annex contains characteristics for heart valve repair systems that should be considered for inclusion in the design documentation. This may include written descriptions and technical drawings as appropriate.

F.2 Characteristics of heart valve repair device

— device identifying name (refer to Annex B for examples);

— available sizes/ configurations, device identifying dimensions, and intended anatomical dimensions;

— components and total number of each (e.g. 2 chords, leaflets, support structure, coating);

— structural materials (e.g. stainless steel, nitinol, titanium, polymer);

— non-structural materials (e.g. pericardium tissue, polymer);

— component-joining materials/methods (e.g. suture materials, adhesives);

— deployment mode or anchoring techniques (e.g. self-expanding, balloon expanding, suturing, antegrade/ retrograde deployment);

— intended implant position (e.g. aortic, mitral, tricuspid, pulmonic, coronary sinus, atrium, papillary muscles, ventricles);

— how the device connects or interacts with the intended implant site, immediately after implantation or progressively post-implantation;

— retrievability;

— repositionability;

— orientability;

— post-implant adjustability;

— locations of radiopaque markers;

— implant sizing;

— inter-device functionality and deployment considerations;

— device storage media.

F.3 Characteristics of delivery system

— delivery approach (e.g. transfemoral, transapical, transseptal, intercostal);

— delivery tools/catheters;

— guidewire;

— introduction sheath;

— balloon;

— crimping/loading tool;

— access port;

— description of the delivery tools/controls in relation to exchange mechanisms involved during implantation (e.g. suturing, description of locking mechanisms);

— additional accessories;

— disposables.

F.4 Chemical treatments, surface modifications, or coatings

Any chemical treatments, surface modifications, or coatings used, including primary fixation of tissue and any anti-calcification, anti-infection, or anti-thrombotic treatments should be documented. For device-drug combination products, elements of ISO 12417 may be applicable.

F.5 Implant procedure

A brief description of the recommended implant procedure or technique, along with implant sizing procedures, should be documented. The manufacturer should describe the environmental conditions under which the implantation procedure is intended to be conducted (e.g. sterile technique, procedure room environment).

NOTE See Reference [40], [41].

F.6 Accessories

Any accessories that are to be used in conjunction with the heart valve repair device and its implantation (e.g. sizers, guidewires, introducer sheaths, balloon catheters, loading tools, etc.) should be described and their materials of construction should be provided.

Annex G
(informative)

Heart valve repair system hazards, associated failure modes and evaluation methods

G.1 General

As outlined in Annex A, this document utilizes a risk-based approach for heart valve repair device design and testing. This risk-based approach requires a comprehensive assessment of the hazards associated with devices under consideration, the appropriate failure modes and methods of evaluating the impact of these hazards as well as efficacy of risk mitigation efforts. This annex provides guidance on the risk-based approach as relevant to heart valve repair devices. In addition, two examples of risk management plans are presented in Tables G.2 and G.3 to demonstrate potential approaches to this assessment. The information presented in this annex is not intended to be all-inclusive.

G.2 Hazards, failure modes, and evaluation methods

Provided below are definitions to essential risk assessment terms:

— Harm - injury or damage to the health of people, or damage to property or the environment [ISO/IEC Guide 51:2014, 3.3; Reference [8]]

— Hazard - potential source of harm [ISO/IEC Guide 51:2014, 3.5; Reference [8]]

— Failure mode – cause of the hazards

Typical hazards, examples of their associated failure modes, and possible evaluation methods are given in Table G.1. This list is not intended to be all-inclusive but representative of hazards and failure modes that are applicable to heart valve repair devices.

NOTE For guidance on how to identify and assess potential device-related use errors, and extensive information about use-related hazards, failure modes, and evaluation methods, see IEC 62366-1, which includes a figure of a comparison of the risk management process (ISO 14971) and the usability engineering process, as well as an informative annex on categories of user action and an informative annex on examples of use errors, abnormal use and possible causes.

Table G.1 — Heart valve repair device possible hazards, associated failure modes and evaluation methods

Hazard	Possible failure mode(s)	Possible evaluation method(s)
Valve stenosis	Pannus overgrowth, excessive device and/or leaflet deformation, device structural deterioration, excessive device recoil, device migration and/or embolisation, adjacent leaflet thickening, device crushing during CPR, incorrect device implantation, implantation of multiple devices	Pulsatile-flow pressure difference, wear/durability testing, device fatigue testing/analysis, device creep testing, device migration testing, device recoil testing, pre-clinical *in vivo* evaluation with echocardiographic characterization, cadaver evaluations, *ex vivo* evaluation, biocompatibility assessment, clinical evaluation
Increased regurgitation	Native leaflet tear, abrasion, delamination or shrinkage, native leaflet prolapse, excessive device deformation, device structural deterioration, suture breakage/pull-out, suture hole elongation, device migration and/or embolisation, device crushing during CPR, incorrect device implantation	Pulsatile flow regurgitation testing, valve prolapse testing, material characterization, device creep testing, durability testing, device fatigue testing/analysis, pre-clinical *in vivo* evaluation with echocardiographic and fluoroscopic characterization, *in vitro* flow visualization, cadaver evaluations, *ex vivo* evaluation, biocompatibility assessment, clinical evaluation
Embolisation of debris – device or procedure related	Device or anatomical fragments resulting from device structural deterioration or generated during device delivery or delivery system fracture, incorrect device implantation	Material characterization, biostability testing, durability testing, device fatigue testing/analysis, pre-clinical *in vivo* evaluation, clinical evaluation
Myocardial infarction	Excessive tissue deformation, coronary artery perforation due to device implantation, coronary artery compression, coronary sinus thrombosis	Anatomical patient model evaluation (e.g. CT reconstruction), pre-clinical *in vivo* evaluation, biocompatibility assessment, device mechanical testing, clinical evaluation
Device embolisation	Fixation failure, improper sizing, device structural deterioration, MRI incompatibility	Device migration testing, durability testing, device fatigue testing/analysis, MRI compatibility evaluations, pre-clinical *in vivo* evaluation, clinical evaluation
Device migration/ partial pull-out	Fixation failure, device structural deterioration, improper sizing	Device migration/ pull-out testing, durability testing, device fatigue testing/analysis, MRI compatibility evaluations, pre-clinical *in vivo* evaluation, clinical evaluation
Haemolysis	Material or mechanical factors that cause elevated shear stresses or disruption of red blood cells	*In vitro* flow visualization, *in vitro* whole blood studies in bench models, computational modelling, pre-clinical *in vivo* evaluation, clinical evaluation, haemocompatibility assessment
Thrombosis, thromboembolism	Material or mechanical factors that cause flow stasis or elevated shear stresses or adverse blood-material interaction	Material characterization, *in vitro* flow visualization, blood loop model, blood-material interaction characterization, computational modelling, pre-clinical *in vivo* evaluation, clinical evaluation, haemocompatibility assessment
Bioincompatibility	Local or systemic toxicity, inappropriate tissue response or effect on coagulation, material degradation, leaching of component compounds	Biological evaluation per ISO 10993-1, material characterization, blood material interaction characterization, biostability testing, leaching testing, corrosion testing, characterization of sterilization residuals, pre-clinical *in vivo* evaluation, clinical evaluation
Infective endocarditis	Non-sterile device, non-sterile accessories	Validation of sterility processes for device and accessories to a sterility assurance level of 10^{-6}, device package integrity testing

Table G.1 *(continued)*

Hazard	Possible failure mode(s)	Possible evaluation method(s)
Inability to complete implant procedure; increased procedural time	Improper patient screening criteria, device or delivery system failure, improper sizing, device damage during shipment, preparation, delivery and retrieval, device not compatible with accessories, system not visible under imaging techniques, use error	Design validation with device, packaging, accessories, and IFU; tracking evaluation of device and delivery system; in-process inspections, pre-clinical *in vivo* evaluation, usability and clinical evaluations
Virus, bovine spongiform encephalopathy or other transmissible agent	Tissue and/or tissue-derived source material contamination	Demonstrated compliance with all elements of the ISO 22442 series
Bleeding	Perforation of vessel wall during device implantation, perforation of the anatomical structures due to device structural deterioration/migration, erosion of vessel wall, incomplete closure of access site, access	Design validation testing, pre-clinical *in vivo* evaluation, clinical evaluation
Unintended anatomical interactions	Valve leaflet interference, coronary sinus occlusion, coronary artery occlusion, conduction system interference, vascular or myocardial injury, chordal entanglement and/or rupture, septal displacement, unintended effects on other heart valves (e.g. aortic insufficiency following mitral valve repair)	*Ex vivo* evaluation (e.g. cadaver studies, isolated heart studies), pre-clinical *in vivo* evaluation, clinical evaluation, anatomical patient model evaluation (e.g. CT reconstruction)
MRI incompatibility	Device migration, device heating, image distortion, poor device visualization	Material characterization, MRI compatibility testing
Device is prematurely deployed	Design or use error	*In vitro* simulated use studies, usability assessment of representative intended users conducting simulated implant procedure tasks, clinical evaluation
Disruption to conduction system	Impact to conduction nodes, particularly during tricuspid/ aortic valve repair	Cadaver evaluations, *ex vivo* evaluation, pre-clinical *in vivo* evaluation, clinical evaluation

Table G.2 — Example of Design Failure Mode and Effects Analysis (DFMEA) approach to a heart valve repair device

DFMEA number:				**Device/System name: Surgically Implanted Rigid Mitral Annuloplasty Ring**						**Prepared by:**		
Design responsibility:				**Part number: 123456**						**Original date:**		
Team members:										**Revision date:**		
ID	**Component**	**Function**	**Failure Mode**	**Effects**	**Cause**	**Initial Assessment**			**Risk Mitigation/ Control Actions**	**After Risk Control**		
						Sev Rank	**Prob Rank**	**Risk Class**		**Refined Sev Rank**	**Refined Prob Rank**	**Residual Risk Class**
1	Ti-6Al-4V structural element	Provide structural reinforcement to mitral valve repair; remodel annulus	Fatigue fracture	Insufficiency, re-operation, explant, peripheral oedema, dilated cardiomyopathy, hypertrophy	Inadequate fatigue margin—*in vivo* loads exceed fatigue capability of component				— Characterization of *in vivo* loading conditions — Design lifetime requirements — Fatigue characterization of structural component material — Device/component fatigue testing — FEA of component under worst-case loading and material conditions			
2	Polyester cloth covering	Provide capability for securely anchoring device within annulus	Suture tear out	Extended operation time to replace device	Insufficient suture retention strength				— Suture retention strength requirements — Suture pull testing — Usability testing — Physician training			

Table G.2 *(continued)*

DFMEA number:				**Device/System name: Surgically Implanted Rigid Mitral Annuloplasty Ring**						**Prepared by:**		
Design responsibility:				**Part number: 123456**						**Original date:**		
Team members:										**Revision date:**		
						Initial Assessment				**After Risk Control**		
ID	**Component**	**Function**	**Failure Mode**	**Effects**	**Cause**	**Sev Rank**	**Prob Rank**	**Risk Class**	**Risk Mitigation/ Control Actions**	**Refined Sev Rank**	**Refined Prob Rank**	**Residual Risk Class**
3	Device holder	Provide capability for securely holding device during implantation	Holder does not release from device post-implant	Extended operation time to remove holder; possible damage to native tissue	Holder is improperly attached to device – suture knot is anchored to cloth covering				— Manufacturing procedure for holder attachment — 100 % inspection of holder attachment — Usability testing — Physician training			
4					Holder design does not facilitate easy cutting of holder attachment sutures *in situ*				— Holder design specification — Usability testing — Physician training — Pre-clinical animal evaluation			

Table G.3 — Example of Hazard analysis approach to a heart valve repair device

Hazard analysis number:				**Device/System name: Surgically Implanted Rigid Mitral Annuloplasty Ring**				**Prepared by:**		
Design responsibility:				**Part number: 123456**				**Original date:**		
Team members:								**Revision date:**		
ID	**Hazard**	**Initiating Events**	**Hazardous Situation**	**Harm**	**Initial Assessment**			**Risk Mitigation/Control Actions**	**After Risk Control**		
					Sev Rank	**Prob Rank**	**Risk Class**		**Refined Sev Rank**	**Refined Prob Rank**	**Residual Risk Class**
1	Device embolisation	Insufficient anchoring of device within implant site	Device dehiscence/ suture pull-out/	Total loss of device function; possible patient death; explant and re-operation required				— Device design specification for anchoring robustness — Device migration testing — Suture pull-out testing — Preclinical *in vivo* evaluation — Ex-vivo/ cadaver testing (must consider patient population for repair – functional vs degenerative)			
2			Flailing device – partial ring dehiscence	Damage to surrounding anatomy (e.g. abrasion of ventricles, atria)				-			
3	Excessive residual regurgitation – procedural failure	Incorrect sizing / oversized device implanted	Improper leaflet coaptation immediately post-implant	Ineffective repair resulting in insufficiency; extended operation time to correct repair				— Device sizing and associated accuracy requirements — Usability testing — Pre-clinical animal evaluation with echo characterization — Physician training			

Table G.3 *(continued)*

Hazard analysis number:				**Device/System name: Surgically Implanted Rigid Mitral Annuloplasty Ring**				**Prepared by:**		
Design responsibility:				**Part number: 123456**				**Original date:**		
Team members:								**Revision date:**		
ID	**Hazard**	**Initiating Events**	**Hazardous Situation**	**Harm**	**Initial Assessment**			**Risk Mitigation/Control Actions**	**After Risk Control**		
					Sev Rank	**Prob Rank**	**Risk Class**		**Refined Sev Rank**	**Refined Prob Rank**	**Residual Risk Class**
4	Excessive regurgitation – functional failure	*in vivo* loads exceed design capability of structural component	Device fatigue failure resulting in improper leaflet coaptation	Insufficiency, re-operation, explant, peripheral oedema, dilated cardiomyopathy, hypertrophy				— Characterization of *in vivo* loading conditions — Design lifetime requirements — Mechanical device/component static/fatigue testing — FEA — Mechanical wear testing (simulate interactions between device and native anatomy)			

Table G.3 *(continued)*

Hazard analysis number:				**Device/System name: Surgically Implanted Rigid Mitral Annuloplasty Ring**				**Prepared by:**		
Design responsibility:				**Part number: 123456**				**Original date:**		
Team members:								**Revision date:**		
ID	**Hazard**	**Initiating Events**	**Hazardous Situation**	**Harm**	**Initial Assessment**			**Risk Mitigation/Control Actions**	**After Risk Control**		
					Sev Rank	**Prob Rank**	**Risk Class**		**Refined Sev Rank**	**Refined Prob Rank**	**Residual Risk Class**
5	Bioincompatibility	Inadequate cleaning process post-device manufacture	Leaching of chemical residuals into tissue/blood stream	Local or systemic toxicity resulting in infection; death				— Component cleaning requirements post-manufacture — In process monitoring of devices post-manufacture — Biocompatibility safety evaluation per applicable ISO Standard — Material characterization — Blood material interaction characterization — Biostability testing — Corrosion testing — Characterization of residuals — Pre-clinical animal evaluation			

G.3 Failure modes/ hazards related to the delivery system

G.3.1 Relating to the delivery system's "Ability to access" include, but are not limited to, the following:

a) guidewire not crossing the lesion;

b) introducer and delivery systems not matching the access site (i.e. size mismatch);

c) delivery system not advancing to target implant site;

d) emboli generation;

e) device embolisation from the delivery system;

f) vessel dissection;

g) myocardial perforation;

h) persistent septal defect;

i) access site complications.

G.3.2 Relating to the "Ability to deploy the delivery system" include, but are not limited to, the following:

a) inability to fully and properly deploy the device;

b) disproportionate dimensions and properties, such as balloon compliance and burst pressure, of balloon relative to device and implant site (if applicable);

c) device embolisation from the delivery system;

d) balloon failure (if applicable);

e) damage of device components by other components;

f) inadequate visualization;

g) emboli generation.

G.3.3 Relating to the "Ability to withdraw the delivery system" include, but are not limited to, the following:

a) improper balloon deflation (balloon expandable);

b) balloon winging (cross sectional shape of the balloon when deflated that can cause problems during withdrawal);

c) lack of structural integrity;

d) emboli generation;

e) diameter mismatch;

f) device embolisation from the delivery system;

g) damage of device system components by other components;

h) delivery system snags on the device;

i) inadequate visualization;

j) device embolisation;

k) inability to remove removable device system components.

G.3.4 Relating to the "Haemostasis of the delivery system" include, but are not limited to, the following:

a) size mismatch;

b) seal incompetence;

c) other leakage;

d) haemostasis of the access vessel;

e) damage to the vascular access site.

G.3.5 Relating to the "Ability to accurately deploy the device" within the target implant site include, but are not limited to, the following:

a) inaccurate positioning or orientation;

b) improper deployment configuration;

c) incomplete deployment;

d) inadequate visualization;

e) improper sizing of implant site.

G.3.6 Relating to "Effective fixation of the device" within the vasculature include, but are not limited to, the following:

a) incomplete apposition to vessel wall;

b) excessive or inadequate radial outward force;

c) improper sizing of implant site;

d) device migration;

e) device embolisation.

G.3.7 Related to "loss of structural integrity and/or durability of the device" include, but are not limited to, the following:

a) structural failure of implant;

b) loss of complete apposition to vessel wall;

c) leaking;

d) perforation;

e) device migration;

f) device embolisation;

g) thrombogenesis;

h) potential failure modes, such as wear, strut fracture, loss of fixation, delamination, and suture breaks.

G.4 Additional generic failure modes and causes

Additional generic failure modes and causes include:

— heart valve repair device and delivery system cannot navigate tortuous anatomy;

— heart valve repair device cannot be loaded onto delivery system (if applicable);

— heart valve repair device misloaded on delivery system;

— heart valve repair device cannot be released from delivery system post-deployment;

— heart valve repair device cannot be recaptured or repositioned (if appropriate);

— instructions for use inadequate;

— poorly designed delivery system user interface;

— inadequate labelling;

— inadequate warnings;

— use by unskilled/improperly trained personnel;

— lack of adherence to sterile conditions during implantation;

— packaging damaged during shipment;

— shelf life degradation;

— environmental damage during shipment and storage (excess heat or cold);

— improper re-use of device.

Annex H
(informative)

In vitro test guidelines for paediatric devices

H.1 Introduction and paediatric definitions

Traditionally, heart valve repair devices have been designed, tested, and labelled for the adult population. Many real and perceived scientific, marketing, and regulatory barriers have limited the development of paediatric heart valve repair devices. These include the need for small device sizes, patient growth requiring multiple reoperations, problems with enhanced calcification of tissue components, a perceived small market size, and a lack of sufficient patients to fill a typical clinical investigation. These questions were addressed at a Paediatric Heart Valve Workshop held in Washington, DC in January 12, 2010, which was attended by clinicians, device industry representatives, academicians, and the United States (US) Food and Drug Administration (FDA) (see Reference [36]). The following guidelines for *in vitro* testing of devices intended for the paediatric population are from a publication based on that workshop (See Reference [44]).

Some definitions of paediatrics include only four groups (newborn, infant, child, adolescent), but input from paediatric clinicians led to adding the "toddler" subpopulation.

Table H.1 — Paediatric definitions

Paediatric subpopulation	Proposed definition
Newborn	0 < age < 30 days
Infant	30 days ≤ age < 1 year
Toddler	1 year ≤ age < 5 years
Child	5 years ≤ age < 13 years
Adolescent	13 years ≤ age < 22 years

H.2 Pulsatile flow test conditions

Table H.2 — Pulsatile flow test conditions: left side

Paediatric subpopulation	Systolic duration %	MAP mmHg	Beat rate beats/min	Cardiac output l/min
Newborn	50	45	60, 150, 200	0,3; 1; 1,5
Infant	50	55	60, 120, 200	0,5; 2; 3
Toddler	45	65	60, 100, 160	1,5; 3; 4.5
Child	40	80	60, 80, 140	2; 3,5; 5
Adolescent	35	100	45, 70, 120	2, 5, 7

Table H.3 — Pulsatile flow test conditions: right side

Paediatric subpopulation	Systolic duration %	MAP mmHg	Beat rate beats/min	Cardiac output l/min
Newborn	50	20	60, 150, 200	0,3; 1; 1,5
Infant	50	20	60, 120, 200	0,5; 2; 3
Toddler	45	20	60, 100, 160	1,5; 3; 4,5
Child	40	20	60, 80, 140	2; 3,5; 5
Adolescent	35	20	45, 70, 120	2, 5, 7

H.3 FEA/life analysis conditions

Table H.4 — FEA/life analysis conditions: left side

Paediatric subpopulation	FEA peak differential pressure/CO mmHg/l/min	Life analysis cycle criterion (equivalent years)
Newborn	90/1,5	5
Infant	100/3	7
Toddler	110/4,5	10
Child	135/5	10 [a]
Adolescent	160/7	10 [a]
[a] Reference [44] says 15 equivalent years, which comes from US. FDA.		

Table H.5 — FEA/life analysis conditions: right side

Paediatric subpopulation	FEA peak differential pressure/CO mmHg/l/min	Life analysis cycle criterion (equivalent years)
Newborn	40/1,5	5
Infant	40/3	7
Toddler	40/4,5	10
Child	35/5	10 [a]
Adolescent	40/7	10 [a]
[a] Reference [44] says 15 equivalent years, which comes from US. FDA.		

Annex I
(informative)

Examples and definitions of some physical and material properties of heart valve repair device components

I.1 General

This annex provides examples and definitions of the physical and material properties that could be relevant in characterizing a heart valve repair device and/or its components.

All measurements should be performed on materials or components as they would be found in the finished product. This includes all subsequent treatments after fabrication.

Examples of some standards that could be relevant for physical and material property characterization are provided in Annex J.

The risk analysis should play a role in the choice of determining the physical and material properties of the heart valve repair device and its components.

I.2 Bulk physical properties

I.2.1

biostability

change in chemical composition of a material after exposure to a physiologic-fluid environment

I.2.2

chemical composition

measurement of the chemical composition and purity, including any processing aids

I.2.3

coefficient of thermal expansion

change in physical dimension as a result of a change in temperature

I.2.4

density

measurement of the mass per unit volume, i.e. the compactness of a material

I.2.5

film composition

analysis of the elemental composition of a film, expressed as a percentage

I.2.6

film thickness

thickness of a film deposited on a substrate averaged over the surface of the film

Note 1 to entry Techniques for measuring thin-film thickness include profilometry and ellipsometry. In some cases, Auger depth profiling can be used.

I.2.7

glass transition temperature

characteristic temperature of a polymer system below which long-chain mobility no longer exists

I.2.8

hydraulic expansion

comparison of the dimensions of the material before and after exposure to water

I.2.9

liquid diffusivity (porosity and permeability)

measurement of the ability of a material to absorb or adsorb biological components from the surrounding tissues and fluid environments

Note 1 to entry This biological property could cause calcification and premature failure of some animal tissues under certain stresses.

I.2.10

material hardness

measurement of resistance to scratching or plastic deformation by indentation (generally related to wear resistance)

I.2.11

melt index

number of grams of thermoplastic resin at a specified temperature that can be forced through a specified orifice in an allotted time by a specified pressure

I.2.12

melting point

temperature at which a solid material turns liquid

I.2.13

microstructure

size and shape of the grains, defects, voids, etc. of which the material is composed.

Note 1 to entry For tissue-derived materials, this should include cellular or extracellular matrix material (e.g. collagen, elastin) morphology.

I.3 Surface physical properties

I.3.1 General

All measurements should be performed on materials or components as they would be found in the finished product. This includes all subsequent treatments after fabrication, for example, sterilization.

I.3.2

critical surface tension

surface tension at which a liquid spreads on a substrate for complete wetting

Note 1 to entry Surface roughness and chemical composition play a key role in how an implant interacts with the biological host. Critical surface tension is a useful attribute for characterizing the surface of a solid material. The measurement is affected by the surface's topology, chemistry and cleanliness. The measurements are related to the surface free energy of the material.

I.3.3

surface charge and surface charge density

type of charge (positive or negative) and the amount that can be bound to the surface of a material

Note 1 to entry It has been suggested that surface charge can play an important role in the biocompatibility of materials.

I.3.4

surface chemical composition

material composition within a few atomic layers of the surface

Note 1 to entry Variations in the chemicals present at the surface could affect how a material will react with the host. The chemical constituents of the surface can be altered by manufacturing processes such as grinding, polishing, cleaning, sterilizing and handling.

I.3.5

surface resistance

R

ratio of the bulk resistivity and film thickness

Note 1 to entry $R_{\text{sheet}} = \frac{\Omega}{\delta}$

where

Ω is the bulk resistivity, expressed in ohm-centimetres;

δ is the sample thickness, expressed in centimetres.

Note 2 to entry A typical method for determining the sheet resistance is the “four-point probe” method. Such measurements are done at several places on the surface of the film to obtain an average sheet resistance value.

I.3.6

surface roughness

microtopology of the component surface

I.4 Mechanical and chemical engineering properties

I.4.1

General

The most commonly utilized mechanical properties are indicated with a star (*) in this list below.

I.4.2

coefficient of friction

energy expended in moving two components past one another that are in intimate contact

I.4.3

compressive strength*

stress required to deform a material in a uniaxial compressive stress state

Note 1 to entry There can be considerable variation in the measured strength among specimens in these tests. To ensure that the data are representative of the true strength of the material, the results are reported using an appropriate statistical method.

I.4.4

corrosion fatigue

simultaneous action of cyclic stress and chemical attack on a metallic part

I.4.5

crack growth velocity

speed and load conditions under which a crack will propagate through a material once it has been initiated

Note 1 to entry The rates can be influenced by the residual stresses in the material.

I.4.6

creep

temporal change in dimension of a material under a prescribed, sustained mechanical loading condition

I.4.7

crevice corrosion

corrosion occurring in spaces (crevices) to which the access of the working fluid from the environment is limited

I.4.8

critical stress intensity factor

k_c

stress intensity above which a crack will advance under monotonic, quasi-static loading conditions

Note 1 to entry k_c is a function of the mode of loading, chemical environment, microstructure, test temperature, strain rate and stress state.

I.4.9

dynamic moduli

complex moduli (storage and loss moduli) that describe the mechanical behaviour of viscoelastic materials

I.4.10

fatigue*

fracture of a material under repeated application of a stress or strain

I.4.11

fatigue life*

number of cycles or total time a material can be repeatedly loaded without fracture under specified loading conditions

Note 1 to entry In general, there are two independent time components to fatigue failure. First is the crack initiation phase, when repeated loading cycles weaken a material, usually through a defect coalescence process at a flaw site, until a critical flaw size is reached and fracture occurs. Once a crack is initiated, the second, or crack growth, phase of fatigue begins. The crack continues to grow under repeated loading conditions until the stress loading exceeds the fracture toughness, resulting in total failure.

I.4.12

flexural strength*

stress level required to cause fracture in bending

Note 1 to entry There usually is considerable variation in the measured strength among specimens in these tests. To ensure that the data are representative of the true strength of the material, the results are reported using an appropriate statistical method.

I.4.13

fracture toughness

measure of the ability of a material to deform plastically without fracturing in the presence of a crack

Note 1 to entry This is the stress intensity at which unstable crack growth will proceed.

I.4.14

fretting

surface damage that results when two surfaces in contact experience slight periodic relative motions

I.4.15

fretting corrosion

form of corrosion in which two surfaces rubbing against each other produce small particles which oxidize to form an abrasive powder that exacerbates the destructive process, eventually forming a crack

Note 1 to entry The surface damage occurs between adjacent surfaces that are in close contact, under pressure, and are subjected to slight relative motions.

I.4.16

galvanic corrosion

electrochemical process in which one metal corrodes preferentially when in electrical contact with a different metal and both metals are immersed in an electrolyte

I.4.17

general corrosion

uniform degradation of the surface of a metal due to chemical reactions with specific environments

I.4.18

intergranular corrosion

form of corrosion where the grain boundaries of a metal are more susceptible to corrosion than the matrix

I.4.19

peel strength

adhesion between different layers of a material, usually a lamellar composite

Note 1 to entry Lamellae could include thin surface layers used to change the chemical boundary conditions of a material.

I.4.20

pitting corrosion

form of extremely localized corrosion that leads to the creation and propagation of small holes in the metal

I.4.21

Poisson's ratio*

ratio of change in dimensions in the transverse direction to the longitudinal direction

Note 1 to entry When a piece of material is stretched or compressed longitudinally under a uniaxial load, it changes shape transversely. As with Young's modulus, Poisson's ratio is needed to model the mechanical behaviour of completed devices.

I.4.22

residual stress

stresses that remain in a material after it has been fabricated when there is no loading applied

Note 1 to entry Residual stress can be a result of device fabrication process, or native tissue growth and remodelling

I.4.23

strain energy to failure

strain energy needed to deform a material to the breaking point

Note 1 to entry Strain energy is the potential energy stored in a body by virtue of an elastic deformation, equal to the work that must be done to produce this deformation. Strain energy is a measure of the toughness of a material, generally in the absence of a durability mechanism.

I.4.24

stress corrosion cracking

failure of a metal from the combined effects of a corrosion environment and a static tensile stress

I.4.25

stress intensity factor

k

description of the intensity of the stress field ahead of a sharp crack under linear elastic loading conditions

I.4.26

stress relaxation

gradual decrease in measured stress under a specified, sustained elongation or deformation

I.4.27

tear strength*

force needed to initiate or continue tearing a sheet of fabric

I.4.28

tensile strain to failure (elongation)*

total amount of strain that a material can tolerate just prior to failure

I.4.29

tensile strength*

stress required to deform a material in an uniaxial tensile stress state

Note 1 to entry The term “tensile strength” or “ultimate tensile strength” is usually used to define the load carrying capability of a material in a uniaxial tensile stress state typically expressed as an engineering stress. This condition also defines the limit of uniform strain, after which plastic instability (necking) occurs.

Note 2 to entry There is usually considerable variation in the measured strength among specimens in these types of tests. To ensure that the data are representative of the true strength of the material, the results are reported using an appropriate statistical method.

I.4.30

ultimate tensile strength*

UTS

maximum load carrying capability of a sample tested in uniaxial tension

I.4.31

void concentration

number of voids in a film (areas where the film did not cover the substrate) per unit area

Note 1 to entry The void concentration is specific to the void size or range of sizes (e.g. a void concentration might be 100 voids of diameter 1 µm or less per square centimetre).

I.4.32

wear resistance

rate of the systematic removal of material as two surfaces move past one another

I.4.33

Young's modulus*

slope of the initial linear portion of the stress strain curve; a measure of the mechanical stiffness of a material

Note 1 to entry As a tensile or compressive stress is exerted on a piece of material, it tends to elongate or contract. The ratio of the applied stress to the percentage change in length (strain) is defined as Young's modulus. Young's modulus is needed in theoretical modelling of both the static and dynamic stress distributions anticipated in completed devices.

I.5 Nitinol properties

I.5.1 General

The most commonly utilized properties of nitinol are indicated with a star herein.

I.5.2

austenite finish temperature

A_f*

temperature at which the reverse martensite-to-austenite transformation is completed on heating in a single-stage transformation, or the temperature at which the R-phase-to-austenite transformation is completed on heating in a two-stage transformation

Note 1 to entry ASTM defines different methods for determining A_f (e.g. DSC or bend and free recovery).

I.5.2.1

bend and free recovery

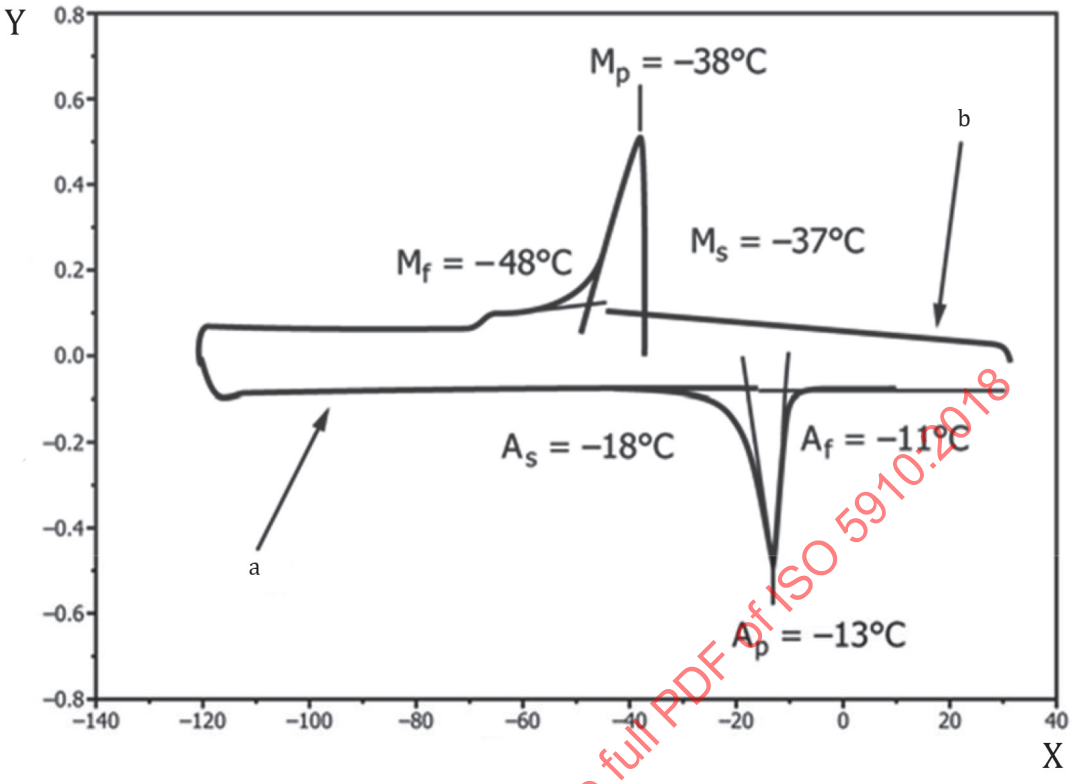
test method to determine the transition temperatures of nitinol by measuring the rate of strain recovery as a function of temperature during heating of a previously deformed test sample

I.5.2.2

differential scanning calorimetry

DSC

test method to determine the transition temperatures of nitinol by comparing the enthalpy (heat evolved) of a test sample to a known standard during heating



Key

As	Austenite start temperature
Ap	Austenite peak temperature
Af	Austenite finish temperature
Ms	Martensite start temperature
Mp	Martensite peak temperature
Mf	Martensite finish temperature
a	Heating.
b	Cooling.

Figure I.1 — Example DSC graph for single-stage transformation nickel-titanium alloy (Reprinted from ASTM F2005 with permission of ASTM International)

I.5.3 Mechanical properties

I.5.3.1

austenite modulus*

steepest part of the initial loading stress-strain curve of a superelastic nitinol sample

Note 1 to entry Unlike most metals the modulus of nitinol can exhibit significant temperature sensitivity and might be affected by the onset of a mechanically-induced transition to the R-phase.

I.5.3.2

lower plateau strength

LPS*

stress at 2.5 % strain during unloading of the sample, after loading to 6 % strain

Note 1 to entry See ASTM F2516.

I.5.3.3

martensite modulus*

steepest part of the unloading stress-strain curve of a superelastic nitinol sample

I.5.3.4

residual elongation

El_r [%]

difference between the strain at a stress of 7,0 MPa during unloading and the strain at a stress of 7,0 MPa during loading

NOTE See ASTM F2516.

I.5.3.5

uniform elongation

El_u [%]

elongation at the maximum force sustained by the test piece just prior to necking, or fracture, or both

Note 1 to entry See ASTM F2516.

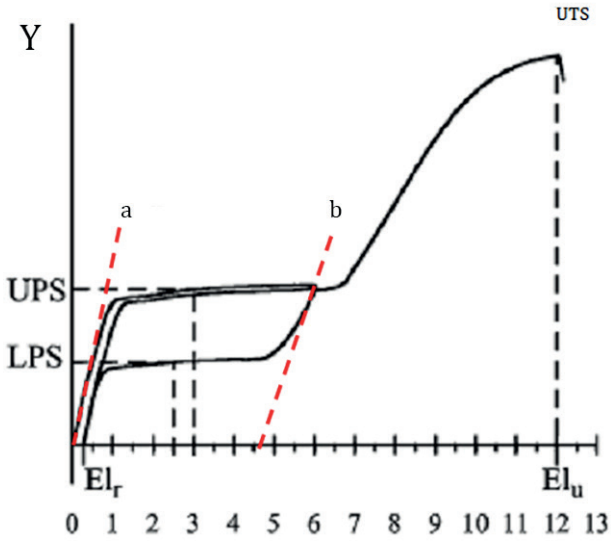
I.5.3.6

upper plateau strength

UPS*

stress at 3 % strain during loading of the sample

Note 1 to entry See ASTM F2516.



Key

Elr residual elongation
Elu uniform elongation
LPS lower plateau strength
UPS upper plateau strength
UTS ultimate tensile strength
a Austenite modulus.
b Martensite modulus.

Figure I.2 — Typical stress-strain curve of superelastic (SE) nitinol indicating various reportable parameters (Reprinted from ASTM F2516 with permission of ASTM International)

I.5.4 Glossary of terms related to nitinol

I.5.4.1

austenite

high-temperature solid phase of approximately equiatomic composition in the Ni-Ti alloy system

Note 1 to entry After processing to obtain specific properties the austenite phase can undergo a reversible phase transformation to the martensitic or rhombohedral (R)-phases.

I.5.4.2

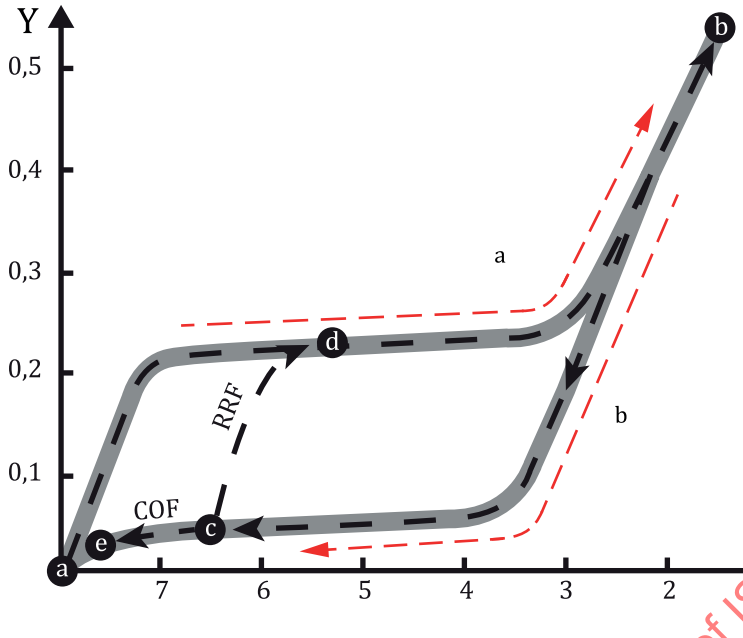
chronic outward force

COF

force exerted by the support structure as it expands to its relaxed diameter after being radially compressed.

Note 1 to entry For an implanted device, the COF is the force exerted by the support structure in its deployed configuration.

Note 2 to entry See Figure I.3.



Key

COF chronic outward force

RRF radial resistive force

a Loading: crimping into catheter.

b Unloading: release from catheter.

Figure I.3 — Force-diameter curve of a superelastic (SE) nitinol support structure; see Reference [16]

I.5.4.3

martensite

low-temperature solid phase of approximately equiatomic composition in the Ni-Ti alloy system that formed from the austenite or the rhombohedral phase with either B19 (orthorombic) or B19' monoclinic crystal structure

I.5.4.4

nitinol

generic trade name for a Ni-Ti alloy (include typical composition range per ASTM) primarily used for its superelastic or shape memory behaviour

I.5.4.5

phase transformation temperature

temperatures related to nitinol

I.5.4.5.1

martensite start temperature

M_s

temperature at which the forward austenite-to-martensite or R–phase-to-martensite transformation begins

I.5.4.5.2

martensite finish temperature

M_f

temperature at which the forward austenite-to-martensite or R–phase-to-martensite transformation ends

I.5.4.5.3

austenite start temperature

A_s

temperature at which the reverse martensite-to-austenite or R–phase-to-austenite transformation begins

I.5.4.5.4

rhombohedral (R-phase) start temperature

R_s

temperature at which the forward austenite-to-R–phase transformation begins

I.5.4.5.5

rhombohedral (R-phase) finish temperature

R_f

temperature at which the forward austenite-to-R–phase transformation ends

I.5.4.6

radial resistive force

RRF

force exerted by a superelastic nitinol support structure as it resists radial compression from its relaxed diameter

Note 1 to entry See Figure I.3.

I.5.4.7

rhombohedral (R) phase

metastable phase of nitinol

I.5.4.8

shape memory alloy

metal which, after an apparent plastic deformation in the martensitic phase, undergoes a thermoelastic phase transformation when heated through its transformation temperature range resulting in a recovery of the deformation

I.5.4.9

superelasticity

nonlinear recoverable deformation behaviour of Ni-Ti shape memory alloys at temperatures above the austenite finish temperature (A_f)

Note 1 to entry The nonlinear deformation arises from the stress induced formation of martensite on loading and the spontaneous reversion of this crystal structure to austenite upon unloading.

Annex J
(informative)

Examples of standards applicable to testing of materials and components of heart valve repair devices

J.1 Metals

J.1.1 Specifications for materials for metal implants

ISO 5832-1, *Implants for surgery — Metallic materials — Part 1: Wrought stainless steel*

ISO 5832-2, *Implants for surgery — Metallic materials — Part 2: Unalloyed titanium*

ISO 5832-3, *Implants for surgery — Metallic materials — Part 3: Wrought titanium 6-aluminium 4-vanadium alloy*

ISO 5832-4, *Implants for surgery — Metallic materials — Part 4: Cobalt-chromium-molybdenum casting alloy*

ISO 5832-5, *Implants for surgery — Metallic materials — Part 5: Wrought cobalt-chromium-tungsten-nickel alloy*

ISO 5832-6, *Implants for surgery — Metallic materials — Part 6: Wrought cobalt-nickel-chromium-molybdenum alloy*

ISO 5832-7, *Implants for surgery — Metallic materials — Part 7: Forgeable and cold-formed cobalt-chromium-nickel-molybdenum-iron alloy*

ISO 5832-8, *Implants for surgery — Metallic materials — Part 8: Wrought cobalt-nickel-chromium-molybdenum-tungsten-iron alloy*

ASTM F2005, *Standard terminology for nickel-titanium shape memory alloys*

ASTM F2063, *Standard specifications for wrought nickel-titanium shape memory alloys for medical devices and surgical implants*

ASTM F2082, *Standard test method for determination of transformation temperature of nickel-titanium shape memory alloys by bend and free recovery*

ASTM F2004, *Standard test method for determination of transformation temperature of nickel-titanium shape memory alloys by thermal analysis*

ASTM F2516, *Standard test method for tension testing of nickel-titanium superelastic materials*

ASTM F2633, *Standard Specification for Wrought Seamless Nickel-Titanium Shape Memory Alloy Tube for Medical Devices and Surgical Implants*

J.1.2 Tensile test with extensometer to failure

ASTM E8, *Standard test methods for tension testing of metallic materials*

ASTM E111, *Standard Test Method for Young's Modulus, Tangent Modulus, and Chord Modulus*

J.1.3 Poisson's ratio

ASTM E132, *Standard test method for Poisson's ratio at room temperature*

J.1.4 Durability crack initiation and endurance limit; S-N curves

ASTM E466, *Standard practice for conducting constant amplitude axial fatigue test of metallic materials*

ASTM E468, *Standard practice for presentation of constant amplitude fatigue test results for metallic materials*

ASTM E739, *Standard practice for statistical analysis of linear or linearized stress-life (S-N) and strain-life (E-N) fatigue data*

J.1.5 Fatigue crack growth rate; crack growth velocity

ASTM E647, *Standard test method for measurement of fatigue crack growth rates*

J.1.6 Hardness

ISO 6508-1, *Metallic materials — Rockwell hardness test — Part 1: Test method (scales A, B, C, D, E, F, G, H, K, N, T)*

ISO 6507-1, *Metallic materials — Vickers hardness test — Part 1: Test method*

J.1.7 Microstructure

ASTM E3, *Standard guide for preparation of metallographic specimens*

ASTM E112, *Standard test methods for determining average grain size*

J.1.8 Thermal expansion

ASTM E228, *Linear thermal expansion of solid materials with a vitreous silica dilatometer*

J.1.9 Fracture toughness

ASTM E399, *Standard test method for plane-strain fracture toughness of metallic materials*

ASTM 1820, *Standard test method for measurement of fracture toughness*

J.1.10 Fatigue life

ASTM E466, *Standard practice for conducting force controlled constant amplitude axial fatigue tests of metallic materials*

ASTM E468, *Standard practice for presentation of constant amplitude fatigue test results for metallic materials*

ASTM E739, *Standard practice for statistical analysis of linear or linearized stress-life (S-N) and strain-life (E-N) fatigue data*

J.1.11 Corrosion

ASTM F2129, *Standard test method for conducting cyclic potentiodynamic polarization measurements to determine the corrosion susceptibility of small implant devices*

ASTM G46, *Standard guide for examination and evaluation of pitting corrosion*

ASTM F746, *Standard test method for pitting or crevice corrosion of metallic surgical implant materials*

ASTM G61, *Standard test method for conducting cyclic potentiodynamic polarization measurements for localized corrosion susceptibility of iron-, nickel-, or cobalt-based alloys*

ASTM G192-08, *Standard test method for determining the crevice repassivation potential of corrosion-resistant alloys using a potentiodynamic-galvanostatic-potentiostatic technique*

ASTM G82, *Standard guide for development and use of a galvanic series for predicting galvanic corrosion performance*

ASTM G71, *Standard guide for conducting and evaluating galvanic corrosion tests in electrolytes*

ASTM G106 - 89 *Standard practice for verification of algorithm and equipment for electrochemical impedance measurements*

ASTM G161 - 00, *Standard guide for corrosion-related failure analysis*

ASTM G199 – 09, *Standard guide for electrochemical noise measurement*

ASTM G108, *Standard test method for electrochemical reactivation (epr) for detecting sensitization of AISI Type 304 and 304l stainless steels*

ASTM G44, *Standard practice for exposure of metals and alloys by alternate immersion in neutral 3.5 % sodium chloride solution*

ASTM A262, *Standard practices for detecting susceptibility to intergranular attack in austenitic stainless steels*

ASTM F1801-97, *Standard practice for corrosion fatigue testing of metallic implant materials*

ISO 16429, *Implants for surgery — Measurements of open-circuit potential to assess corrosion behaviour of metallic implantable materials and medical devices over extended time periods*

ISO 10993-15, *Identification and quantification of degradation products from metals and alloys*

ASTM F3044-14, *Test Method for Standard Test Method for Evaluating the Potential for Galvanic Corrosion for Medical Implants*

J.2 Polymers

J.2.1 Viscosimetry

ISO 1628-1, *Determination of the viscosity of polymers in dilute solution using capillary viscometers — Part 1: General principles*

ISO 61, Plastics — *Determination of apparent density of moulding material that cannot be poured from a specified funnel*

ISO 3219 *Plastics — Polymers/resins in the liquid state or as emulsions or dispersions — Determination of viscosity using a rotational viscometer with defined shear rate*

J.2.2 Melt flow index

ASTM D1238, *Standard test method for melt flow rates of thermoplastics by extrusion plastometer*

J.2.3 Determination of breaking strength under static load

ISO 13934-1, *Textiles — Tensile properties of fabrics — Part 1: Determination of maximum force and elongation at maximum force using the strip method*

J.2.4 Tensile test with extensometer to failure (if possible)

ASTM D638, *Standard test method for tensile properties of plastics*

ISO 527 series, *Plastics — Determination of tensile properties*

J.2.5 Poisson's ratio

ASTM E132, *Standard test method for Poisson's ratio at room temperature*

J.2.6 Determination of dynamic mechanical properties

ISO 6721-1, *Plastics — Determination of dynamic mechanical properties — Part 1: General principles*

ISO 6721-2, *Plastics — Determination of dynamic mechanical properties — Part 2: Torsion-pendulum method*

J.2.7 Resistance to surface wear

ISO 4586-2, *High-pressure decorative laminates — Sheets made from thermosetting resins — Part 2: Determination of properties*

J.2.8 Resistance to scratch

ISO 1518, *Paints and varnishes — Scratch test*

BS 3962-6, *Assessment of resistance to mechanical damage*

J.2.9 Flexural properties; determination of breaking strength under dynamic bending load

ISO 178, *Plastics — Determination of flexural properties*

J.2.10 Fatigue crack initiation and endurance limit; S-N curves

ASTM E466, *Standard practice for conducting force controlled constant amplitude axial fatigue tests of metallic materials*

ASTM E468, *Practice for presentation of constant amplitude fatigue test results for metallic materials*

J.2.11 Fatigue crack growth rate

ASTM E647, *Test method for measurement of fatigue crack growth rates*

J.2.12 Determination of compressive properties

ISO 604, *Plastics — Determination of compressive properties*

J.2.13 Specification of surgical implants made from high-density silicone elastomer

BS 7253-3, *Non-metallic materials for surgical implants — Specification for surgical implants made of heat-vulcanized silicone elastomer*

J.2.14 Density

ASTM D792, *Standard Test Methods for Density and Specific Gravity (Relative Density) of Plastics by Displacement*

J.2.15 Liquid diffusivity (porosity and permeability; water absorption)

ASTM D570, *Standard test method for water absorption of plastics*

J.2.16 Hardness

ASTM D785, *Standard test method for Rockwell hardness of plastics and electrical insulating materials*

J.2.17 Wear resistance

ASTM D1044, *Standard test methods for resistance of transparent plastics to surface abrasion*

ASTM D4060, *Standard test method for abrasion resistance of organic coatings by the Taber abraser*

J.2.18 Creep

ASTM D2990, *Test methods for tensile, compressive, and flexural creep and creep-rupture of plastics*

J.2.19 Fracture toughness

ASTM E399, Standard test method for plane-strain fracture toughness of metallic materials

ASTM 1820, *Standard test method for measurement of fracture toughness*

J.2.20 Hydraulic expansion

ASTM F1087, *Test methods for linear dimensional stability of a gasket material to moisture*

J.3 Ceramics and carbons

J.3.1 Physical and chemical properties

ISO 6474, *Implants for surgery — Ceramic materials based on high purity alumina*

J.3.2 Fatigue rate

ASTM E647, *Standard test method for measurement of fatigue crack growth rates*

J.3.3 Hardness

ASTM E92, *Standard test method for Vickers hardness of metallic materials*

J.3.4 Thermal expansion

ASTM E228, *Linear thermal expansion of solid materials with a vitreous silica dilatometer*

J.3.5 Fracture toughness

ASTM E399, *Standard test method for plane-strain fracture toughness of metallic materials*

J.4 Plastic materials

J.4.1 Possible adaptation of tensile properties

ISO 527 (all parts), *Plastics — Determination of tensile properties*

J.5 Textiles

J.5.1 Determination of tear-out resistance

ISO 13937-2, *Textiles — Tear properties of fabrics — Part 2: Determination of tear force of trouser-shaped test specimens (Single tear method)*

J.5.2 Determination of water absorption

DIN 53923, *Testing of textiles — Determination of water absorption of textile fabrics*

J.5.3 Determination of breaking strength under static load

ISO 13934-1, *Textiles — Tensile properties of fabrics — Part 1: Determination of maximum force and elongation at maximum force using the strip method*

J.5.4 MRI compatibility

ASTM F2052, *Standard test method for measurement of magnetically induced displacement force on medical devices in the magnetic resonance environment*

ASTM F2119, *Standard test method for evaluation of MR image artefacts from passive implants*

ASTM F2182, *Standard test method for measurement of radio frequency induced heating near passive implants during magnetic resonance imaging*

ASTM F2213, *Standard test method for measurement of magnetically induced torque on medical devices in the magnetic resonance environment*

ASTM F2503, *Standard practice for marking medical devices and other items for safety in the magnetic resonance environment*

Annex K
(informative)

Considerations for device material properties undergoing alterations post implantation

Thermal, biochemical and mechanical properties of the materials of the heart valve repair device may change post-implantation; therefore, there is a need to adequately assess the post-implantation properties of the materials that make up the structure of the implant, where these changes may negatively affect clinical performance of the device.

Post-implantation material properties should be used to assess any changes induced by time, temperature and/or bio-chemical effects to the heart valve repair device, as identified through the risk analysis (e.g. stress analysis using post-implantation material properties). These material property changes should be distinguished from fatigue property changes caused by cyclic loading, which is specified in Annex N and Annex O; however these material properties may also be used to provide a good estimate of material changes in time with fatigue testing if applicable (e.g. bioabsorbable polymers).

See Annex I for relevant mechanical properties that can be addressed pre- and post-implantation.

Annex L
(informative)

Corrosion assessment

L.1 Rationale

Corrosion of the implantable device components can cause or contribute to device failure. In addition, corrosion byproducts (e.g. metallic ion release) could cause biological and tissue responses. *In vitro* testing is performed to detect and assess corrosion susceptibility.

Many types of corrosion mechanisms might act, often simultaneously, on the device over time. While some corrosion mechanisms are predominantly related to material properties, surface finish and manufacturing of the component (e.g. uniform corrosion, pitting corrosion, intergranular corrosion), others relate more to the device design (e.g. crevice corrosion, galvanic corrosion) or the operational conditions (e.g. fretting corrosion, corrosion fatigue, stress corrosion cracking). The planning, selection, design and execution of corrosion tests should ensure that all relevant corrosion mechanisms and their interactions are identified and assessed to evaluate the device performance during its service life. When assessing corrosion test results, non-tested parts are useful in distinguishing between corrosion damage and normal variations in surface finish.

Corrosion assessment can include a variety of electrochemical, microscopic and gravimetric methods. Often combinations of qualitative observations, quantitative measurements, and statistical analyses are needed to provide an overall assessment of corrosion. Standard corrosion tests developed by ASTM, NACE and ISO address the technical requirements specified in the test method but might need to be modified to appropriately address conditions applicable to device applications. If a Standard is followed where no acceptance criteria are prescribed, the manufacturer should justify the final acceptance criteria adopted.

NOTE See Reference [37].

L.2 Introduction

The corrosion mechanisms described below are often applicable to materials and conditions representative of implantable devices, although other mechanisms are possible. The manufacturer should provide a rationale for the selected test methods and justify that all applicable corrosion mechanisms and conditions have been addressed through testing or theoretical assessments. A list of commonly used standard methods is provided in Annex J.

L.3 Pitting corrosion

Pitting corrosion is a localized form of corrosion. It occurs when discrete areas of a material lose their passive state and undergo corrosion attack while the majority of the surface remains unaffected. The localized corrosion attack creates small holes (pits) which can rapidly penetrate the material and contribute to failure. Pitting of a material depends strongly on the presence of aggressive ionic species (e.g. chloride ions) in the environment having a sufficient oxidizing potential.

The assessment of the pitting corrosion susceptibility of the device is of relevance both for storage solution and in simulated *in vivo* conditions. Previous experience with similar devices could be referenced; however, it is necessary to show the surface chemistries between the comparative devices, as the materials, design, and fabrication processes specific to the device under analysis may reduce or eliminate the applicability of the comparative device. For example, the pitting corrosion resistance of

nitinol is sensitive to processing variables such as heat treatment and electropolishing; therefore the pitting corrosion susceptibility of the finished nitinol support structure should be characterized.

Pitting corrosion can be assessed by electrochemical methods, such as potentiodynamic and potentiostatic measurements described in ASTM F2129 and ASTM F746. Crevice corrosion will occur at lower potentials than pitting and therefore interference from crevices on the test sample can lead to an underestimation of the pitting resistance. It is recommended to perform microscopic examination (e.g. as described in ASTM G161) of the samples after testing to evaluate the presence of pits and/or crevice corrosion, because it is difficult to mount a test sample without introducing a crevice at the sample/mount interface.

NOTE See Reference [23].

L.4 Crevice corrosion

Crevice corrosion is a form of localized corrosion which occurs in areas where parts of the material are in contact with small volumes of stagnant liquid. In short, the limited mass transfer within the stagnant liquid in the crevice creates a deoxygenized zone with increased salt and acid concentration compared to the rest of the liquid. This difference shifts the electrochemical potential within the crevice to a more negative value which causes passivity to breakdown and the onset of active dissolution (corrosion).

Crevice corrosion can result from the design of the component or from formation of deposits that introduce a critical crevice. This corrosion mechanism occurs mainly, but not exclusively, on materials which are protected by a passive oxide.

Literature citations or previous experience with similar devices can be relevant. However, as the presence of critical crevices is strongly related to device design, and the material passivity is affected by the specific fabrication processes, generic literature might not be applicable. To capitalize on previous experience with similar devices it is necessary to show that their surface chemistries and crevices are equivalent. Crevice corrosion can be assessed by immersion test methods as well as electrochemical methods under open circuit conditions or applied potential/current, such as described in ASTM F2129, ASTM F746 and ISO 16429.

L.5 Galvanic corrosion

Galvanic (or bimetallic) corrosion is a form of corrosion in which one metal corrodes preferentially when it is in electrical contact with a different metal. Enhanced corrosion of the more negative (less noble) metal will be experienced together with partial or complete cathodic protection of the more positive (more noble) metal.

If the device contains more than one type of metal, such as a support structure with marker bands, the manufacturer should demonstrate the design's resistance to galvanic corrosion. The risk of galvanic corrosion should be addressed at a minimum by theoretical methods, such as the Evans Diagram and ASTM G82. Test methods described in ASTM F3044 or equivalent methods can be used or modified, for example, by incorporating the experimental setup described in ASTM F2129. If overlapping of devices is expected during clinical procedures, then the potential for galvanic corrosion of contacting dissimilar materials should be addressed. Test methods described in ASTM G71 or equivalent methods can be used or modified, by incorporating the experimental setup described in ASTM F2129.

L.6 Corrosion fatigue

Corrosion fatigue can be defined as a materials failure mechanism which depends on the combined action of repeated cyclic stresses and a chemically reactive environment. One example is that localized corrosion-deformation interactions on smooth surfaces act as crack initiation sites at thresholds lower than estimated from linear elastic fracture mechanics. The total damage due to corrosion fatigue is usually greater than the sum of the mechanical and chemical components acting separately.

NOTE See Reference [27].

Crack growth is often rate limited by one of the slow steps in the mass-transport and crack surface reaction sequence and as a consequence, slow loading rates enhance corrosion fatigue damage. Hence, testing at low frequency might be necessary to adequately address the corrosion fatigue mechanisms acting on the device. ASTM F1801 outlines corrosion fatigue testing of standard material specimens for medical implant applications. Corrosion fatigue experiments follow directly from procedures for mechanical tests and can be assessed as part of the fatigue assessment of the device or in separately designed corrosion fatigue tests for the support structure component as justified by the manufacturer.

NOTE See Reference [19].

L.7 Fretting (wear) and fretting corrosion

Fretting is defined as the wear process occurring between contacting surfaces having relative oscillatory motion. Fretting corrosion is caused by corrosion reactions which occur at the interface of two closely fitting surfaces when they are subjected to slight relative oscillatory motion with or without the abrasive effects of corrosion product debris between them.

The potential for fretting (wear) and fretting corrosion should be addressed in designs that allow micromotion between components (e.g. woven wires) that might disrupt an associated coating or passive film.

L.8 Post-fatigue corrosion evaluation

After completion of fatigue testing, specimens should be subjected to detailed microscopic surface inspection for any evidence of corrosion. Recent data indicate that corrosion testing post fatigue and/or device durability testing generally does not provided value over evaluating corrosion on as-manufactured components.

NOTE See Reference [18].

Annex M
(informative)

Guidelines for *in vitro* evaluation of functional performance of the repair

M.1 General

Functional assessment of the repair *in vitro* should evaluate the hydrodynamic performance of the repaired heart valve, using quantitative metrics such as pressure drop, effective orifice area, regurgitant volume and regurgitant fraction. In addition, indicators of valve performance in terms of load to the heart and potential for blood stasis and damage should be assessed. If hydrodynamic assessment of the repair is not feasible or appropriate, functional assessment should be performed using methods that demonstrate the intended action of repair, such as a change in dimension to achieve therapeutic effects.

This annex provides guidance for test equipment, test equipment validation, formulation of test protocols and test methods for evaluating the functional performance of heart valve repairs. Other test methods for evaluating functional performance may be defined by the manufacturer (e.g. appropriately validated computational models). The examples presented in this annex should be utilized as a guide for developing test protocols and reporting results of these alternate tests. Equipment and test procedures should be appropriate for the valve's intended indication, e.g. adult/paediatric, left/right-side. See Table 3 and Table 4, and Annex H for recommended test conditions. The manufacturer should utilize test conditions that simulate the worst case scenario based on an assessment of device function at different test conditions and its impact on native valve. See 7.2.2 for additional information on test conditions and sample selection.

M.2 Steady back-flow leakage testing

M.2.1 Measuring equipment accuracy

M.2.1.1 Steady flow leakage flowrate should have a minimum measurement accuracy of ±1 ml/s.

M.2.1.2 All other measuring equipment should have a minimum measurement accuracy of ±5 % of the full-scale reading.

M.2.2 Test apparatus requirements

M.2.2.1 The steady backflow leakage testing should be conducted in an apparatus that is capable of generating constant back pressures appropriate for the intended device application in accordance with Table 3 and Table 4. See Annex H for guidelines regarding suggested test conditions for the paediatric population.

M.2.2.2 The native heart valve model should be defined by the manufacturer to represent a physiologically relevant condition. Examples of such models are prosthetic valve, *ex vivo* porcine heart valve and *ex vivo* whole heart models.

M.2.2.3 A standardized nozzle in accordance with Figure M.1 can be used to characterize the back pressure, leakage volume flow rate and pressure measuring equipment. A plot of expected values for the backflow standard nozzle gradients can be found in Figure M.2. When accounting for acceptable accuracy tolerances, measured values should agree with these data.

NOTE Results when using physiologic saline with specific gravity of 1,005 g/ml and viscosity of 1,0 cP.

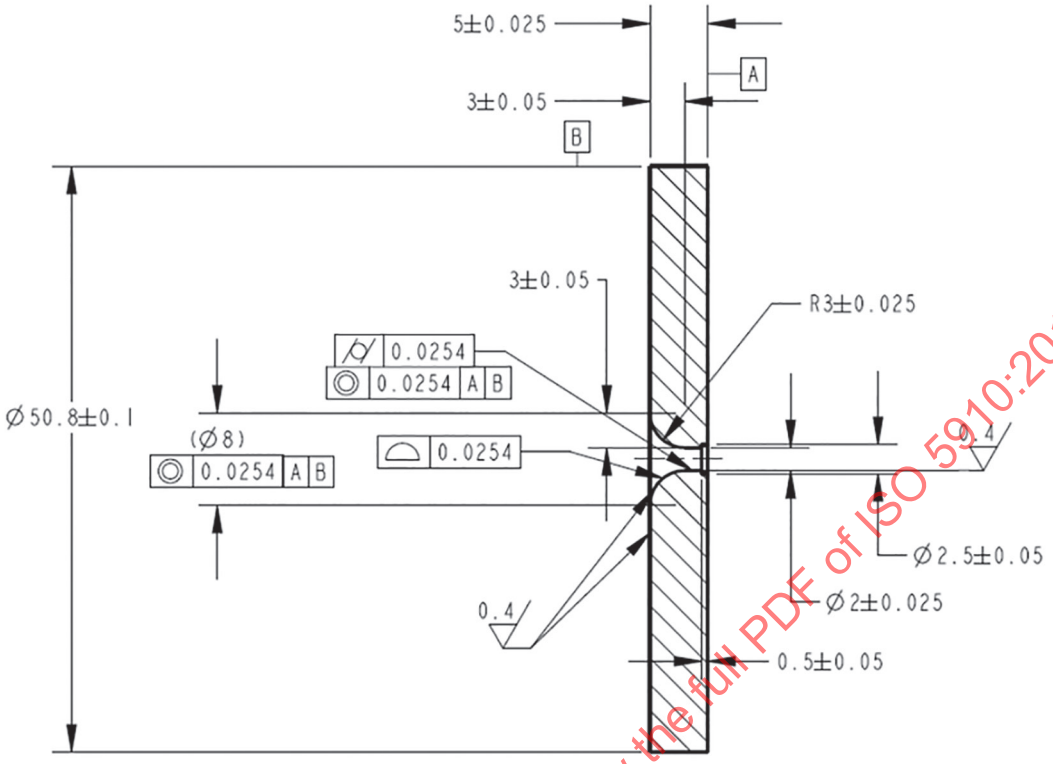


Figure M.1 — Standard nozzle; back flow (dimensions in millimetres)

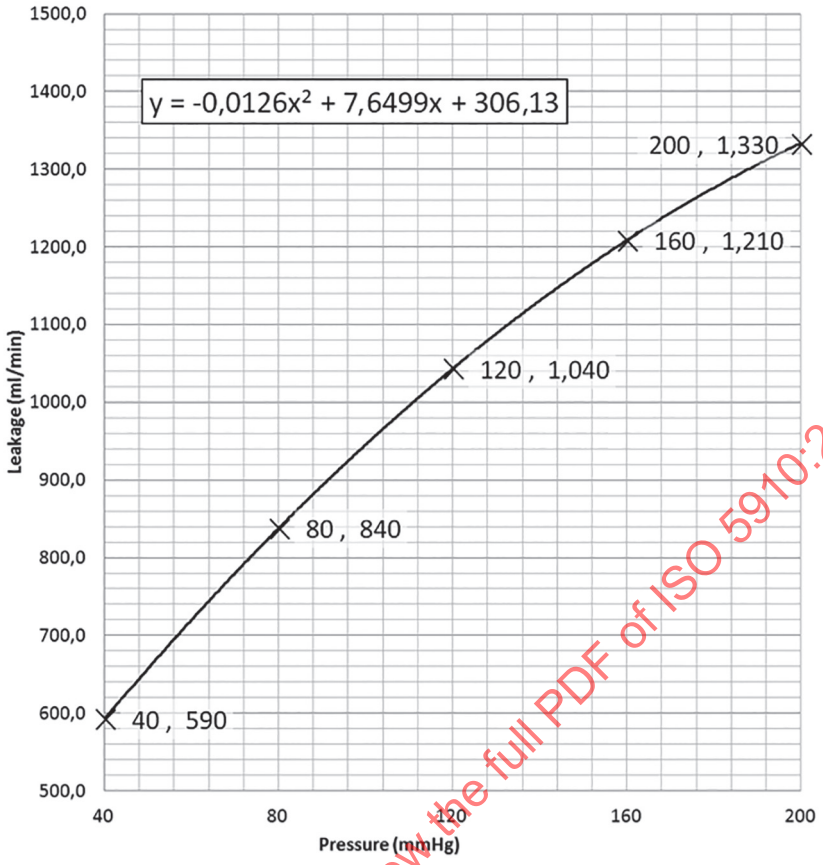


Figure M.2 — Back flow nozzle gradients

M.2.2.4 The repeatability of the test system should be evaluated and documented.

M.2.3 Test procedure

M.2.3.1 Measure the static leakage across the valve before and after repair at a minimum of 3 back pressures appropriate for the intended device application (i.e. hypotensive, normotensive, moderate hypertensive conditions). Collect at least five measurements at each level of back pressure for each valve.

M.2.4 Test report

The steady backflow test report should include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity and density under the test conditions;

b) a description of the steady backflow test apparatus, including calibration of measurement equipment;

c) details of the mean, standard deviation, minimum value and maximum value of the performance test variables at each simulated condition, presented in tabular and graphic form; i.e. static leakage volume flow rate, expressed in l/min, as a function of back pressure.

M.3 Pulsatile-flow testing

M.3.1 Measuring equipment accuracy

M.3.1.1 The pressure measurement system should have an upper frequency limit (−3 dB cut-off) of at least 30 Hz and a differential measurement accuracy of at least ±0,26 kPa (±2 mmHg). The flow meter should have an upper frequency limit (−3 dB cut-off) of at least 30 Hz.

M.3.1.2 Regurgitant volume measurements should have a measurement accuracy of at least ±2 ml.

M.3.1.3 All other measuring equipment should have a measurement accuracy of at least ±5 % of the full-scale reading.

M.3.2 Test apparatus requirements

M.3.2.1 The pulsatile-flow testing should be conducted in a pulse duplicator which produces pressure and flow waveforms that approximate physiological conditions over the required physiological range appropriate for the intended device application in accordance with Table 1 and Table 2. See Annex H for guidelines regarding suggested test conditions for the paediatric population.

M.3.2.2 The test system should permit measurement of time-dependent pressures and volumetric flow rates.

M.3.2.3 The repeatability of the test system should be evaluated and documented.

M.3.2.4 The native heart valve model should be defined by the manufacturer to represent a physiologically relevant condition. Examples of such models are prosthetic valve, *ex vivo* porcine heart valve and *ex vivo* whole heart models.

M.3.2.5 The test system should allow for verification of proper positioning and function of the repair device in the native heart valve model through direct or indirect visualization.

M.3.3 Test procedure

M.3.3.1 Tests should be carried out before and after repair in the position in which it is intended to be used. Qualitative and quantitative assessments should be made.

M.3.3.2 Hydrodynamic measurements should be measured at simulated conditions (i.e. cycle rate, simulated cardiac output, mean back pressure) in accordance with Table 3 and Table 4. See Annex H for guidelines regarding suggested test conditions for the paediatric population. Recommended conditions for heart valve testing are presented below, and these conditions may be appropriate based on intended device application and test system (Reference ISO 5840 series).

M.3.3.3 Pressure difference should be measured at four simulated cardiac outputs between 2 and 7 l/min (e.g. 2; 3,5; 5; 7 l/min), at a single simulated normal heart rate (e.g. 70 beats/min).

M.3.3.4 Regurgitant volumes should be measured at three different pressure conditions representative of hypotensive, normotensive, and severe hypertensive conditions; at three simulated low, normal, and high heart rates; and at a normal simulated cardiac output (see Tables 3 and 4).

M.3.3.5 At least 10 measurements of each of the following variables should be obtained from either consecutive or randomly-selected cycles:

a) mean pressure difference across the test heart valve;

b) mean and RMS flow rates through the test heart valve;

c) forward flow volume;

d) cycle rate;

e) mean arterial pressure over the whole cycle;

f) systolic duration, as a percentage of cycle time;

g) regurgitant volume, including the closing volume, the leakage volume and the corresponding mean pressure difference across the closed valve.

M.3.3.6 Assess the flow fields (velocity and shear) in the immediate vicinity of the test heart valve. Techniques for such measurements include, but are not limited to, laser Doppler velocimetry (LDV), digital particle image velocimetry (DPIV) and computational fluid dynamics (CFD). The CFD code should be verified to make sure that the correct equations and physics are being modelled as applied to the valve design being evaluated. CFD results should be validated by comparison with experimental results.

M.3.3.7 Quantitatively assess the haemolytic and thrombogenic potential of the valve repair device design in each position of intended use, either in the studies described in M.3.3.5, or other relevant *in vitro*, computational and/or *in vivo* studies. Measures such as shear rate magnitude vs. duration and particle residence time should be considered.

M.3.4 Test report

The pulsatile-flow test report should include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity and density under the test conditions;

b) a description of the pulse duplicator, as specified in M.3.2, and its major components and associated apparatus, including a schematic diagram of the system giving the relevant chamber dimensions, chamber compliance (if a compliant chamber is used), details of the location of the pressure-measuring sites relative to the base of the leaflets of the heart valve, pressure measurement instrumentation frequency response, and the appropriate representative pressure and flow waveforms at nominal conditions;

c) an assessment, including appropriate documentation, of the opening and closing action of a test heart valve substitute and, if appropriate, its adjacent flow field under stated conditions;

d) a permanent recording of at least 10 consecutive or randomly selected cycles of the time-dependent simultaneous pressures, proximal and distal to the heart valve, and the volume flow through it. Details of mean, standard deviation, minimum value and maximum value of the following performance test variables at each simulated condition for each test heart valve should be presented in tabular and graphic form:

   — simulated cardiac output;

   — cycle rate;

   — systolic duration, expressed as a percentage of the cycle time;

   — forward flow volume;

   — mean and RMS flow rates;

   — mean pressure difference;

   — effective orifice area (provide formula used);

- regurgitant volume, closing volume and leakage volume, expressed in millilitres and as a percentage of forward flow volume; and the corresponding mean pressure difference across the closed valve;
- mean arterial pressure over the whole cycle;

n) appropriate documentation of proper positioning and function of the repair device in the native heart valve model through direct or indirect visualization;

o) appropriate documentation and quantitative analyses of the velocity and shear stress fields in the immediate vicinity;

p) appropriate qualitative and quantitative documentation for the haemolytic and thrombogenic potential.

Annex N
(informative)

Durability testing

N.1 General

The repair device should be tested under appropriate loads while simulating device function in an appropriate environment and representative target implant site to a specified number of cycles required to demonstrate *in vitro* device durability. This annex specifically refers to device durability, not repair durability, since it might not be possible to conduct durability testing of the repair *in vitro*. For some devices, the same testing may address requirements of both fatigue and durability testing; the manufacturer should justify when this approach is utilized.

This annex provides guidance for formulation of test protocols and test methods for assessing the durability of heart valve repair devices. Other test methods for evaluating durability may be defined by the manufacturer. Equipment and test procedures should be appropriate for the valve's intended indication, e.g. adult/paediatric, left/right-side. See 7.2.2 for additional information on test conditions and sample selection.

N.2 Measurement equipment accuracy

The measurement accuracy and repeatability of the test system should be evaluated and documented. Data sampling rate and natural/ resonant frequency of the measurement equipment should be appropriate to test conditions.

N.3 Test parameters

Tests should be performed at loading levels corresponding to normotensive pressure specified in Table 3 or Table 4. The manufacturer should justify the cycle rate based on the device design and materials of construction as these might influence the results of durability tests.

Particular aspects that can affect the anticipated *in vivo* device lifetime or device properties (e.g. bridge therapy, tissue ingrowth) should be taken into account. Durability testing should be performed for a minimum of 400 million cycles, unless justified when a particular device has a lower anticipated *in vivo* lifetime. Specific devices can experience changes in environment or loading conditions post-implantation (e.g. tissue ingrowth, the manufacturer should take this into account while determining appropriate durability testing durations.

If heart valve repair devices identical in design are intended for use in multiple valve positions, testing should include the loading conditions defined for the worst case valve position. See Annex H for guidelines regarding suggested test conditions for the paediatric population.

N.4 Results evaluation

Some wear is expected on valve repair devices after completing durability testing. Failures, however, are characterized by excessive structural damage and/or functional impairment of the device. A clear definition of “failure” should be established and be consistent with respect to the specific failure mode(s) identified by the risk analysis. Examples of structural deterioration include holes, tears, gross delamination, severing, fraying, incomplete leaflet coaptation of the repaired valve anatomy and/or the heart valve repair device. Examples of functional impairment include excessive regurgitation and/or excessive transvalvular forward flow pressure difference with the repaired heart valve.

N.5 Real time wear testing

In addition to accelerated wear testing, wear testing at physiologic conditions (e.g. beat rates < 200 bpm) may be considered. The results of this testing may be used to evaluate the validity of accelerated durability test results.

N.6 Dynamic Failure Mode

Potential modes of failure associated with heart valve repair deterioration should be identified. A possible evaluation method is to continue testing the valve repairs that have survived the minimum requirements for durability testing until dynamic failure occurs. Other evaluation methods may be employed depending on the device design, materials, and construction. The method(s) used should be justified.

N.7 Report requirements

The durability assessment report should include:

a) a list of the repair devices, including any reference device/ procedure used to conduct the testing;

b) description and dimensions of the implanted repair device;

c) justification for the reference device used, if applicable;

d) justification of the simulated repair (e.g. *ex vivo* mitral annulus evaluation);

e) justification for cycle rates and total simulated cycles used;

f) the pass/fail criteria and justification for the criteria;

g) a description of the fluid used for the assessment, including biological origin or chemical components, temperature, viscosity, pH, and specific gravity under the simulation conditions;

h) descriptions, specifications, and validations of all test apparatus and references to and/or descriptions of any procedures used to complete the assessment;

i) a list of pertinent test conditions (e.g. cycle rate, average peak closed pressure difference), sample pressure waveforms, and rationale for any deviations from those test conditions specified for durability testing;

j) a detailed description of the appearance of the heart valve repair and functional performance prior to test, at the completion of the test, at periodic intervals during the test, and upon the development of structural change and/or failure. Any damage should be characterized by using the appropriate means (e.g. histology of components or surface characterization). It should be indicated if the repairs were intact for the length of the evaluation and if they met the pass/fail criteria.

Annex O
(informative)

Fatigue assessment

O.1 General

Fatigue assessment helps evaluate potential failure modes in the heart valve repair device under physiological and pathological loading conditions. This annex outlines one approach to fatigue assessment, however other approaches to fatigue assessment may also be considered, such as creep modelling and probabilistic methods.

A fatigue assessment may consist of:

— a stress/strain analysis of the structural components and the heart valve repair device under, at a minimum, simulated *in vivo* moderate hypertensive conditions, and other relevant loading modes;

— a fatigue characterization of structural components of the heart valve repair device;

— a fatigue lifetime assessment of the repair components/device.

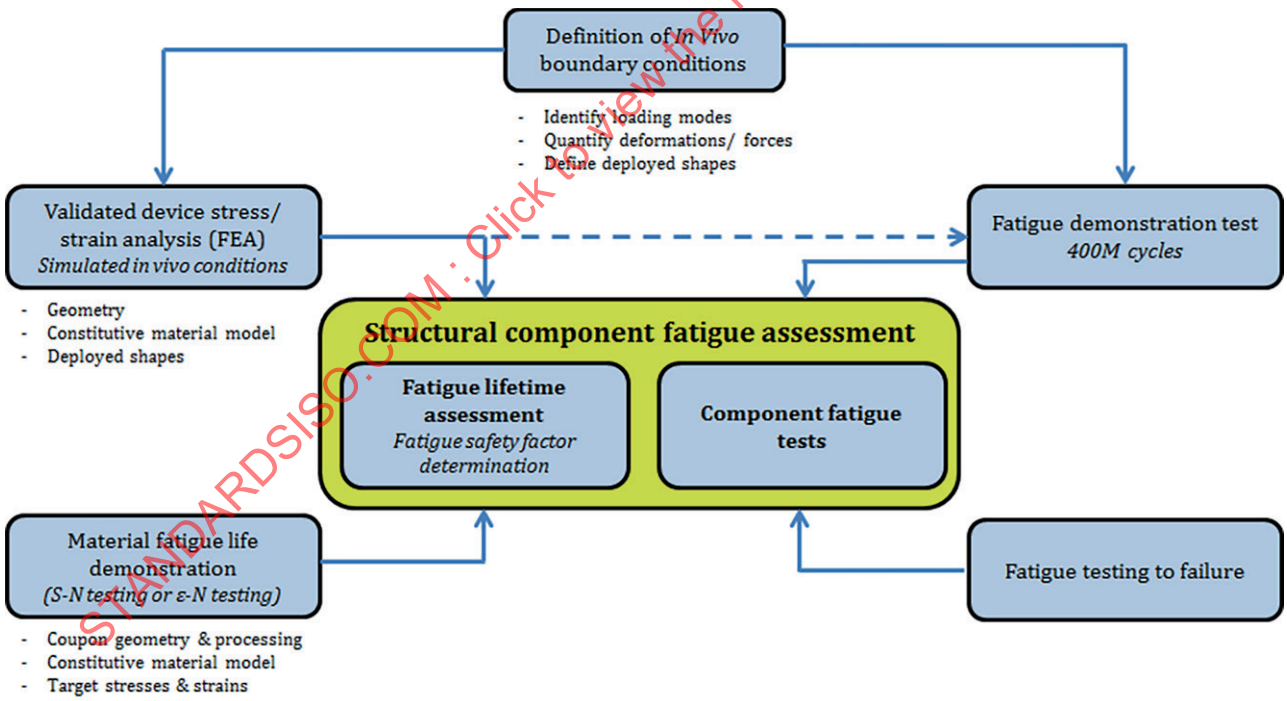


Figure O.1 — Example schematic of a structural component fatigue assessment using a stress or strain-life approach

The selection of stress analysis or strain analysis should be employed depending on the material of the structural component.

O.2 Stress/strain analysis of structural components of the heart valve repair device under simulated *in vivo* conditions

A validated stress/strain analysis (e.g. finite element analysis) under simulated *in vivo* conditions should be performed on key structural components of the repair device, if possible. Other components such as sutures or cloth should be considered for their reaction loads but would not necessarily require analysis.

The analyses should fully represent the range of deployed device configurations and the loading conditions associated with the implantation site. If all possible deployed device configurations are not analysed, it is necessary to conduct an analysis to identify the configuration of the device that have the greatest potential for failure.

Stress/strain analysis should account for all physiologic loading conditions to which the device will be subjected. It might not be feasible to simulate all combined loading modes in a single analysis; however, any de-coupling or superposition of loading modes should be justified. Physiologic loading will depend on the implant site and device design, and may include, but is not limited to:

— differential pressures across the device (minimum pressures associated with moderate hypertensive conditions);

— stresses occurring during valve opening and closing;

— radial dilatation and compression;

— torsion;

— bending;

— axial tension;

— axial compression;

— linear/ transverse compression (e.g. crushing).

These items should be considered in the context of anatomic variability and pathologic changes within the implantation site.

The manufacturer should identify and justify the appropriate *in vivo* loading conditions for the stress-strain analysis. Pressures associated with normal, hypertensive and hypotensive conditions are given in Table 3 and Table 4. See Annex H for guidelines regarding suggested test conditions for the paediatric population.

The entire stress/strain history of the device in each loading step should be considered in the stress/strain analysis. The entire stress/strain history may include, but is not limited to:

— initial fabrication, manufacturing, test, inspection, sterilization, shipping, and storage;

— crimping/loading onto the delivery system;

— deployment/ implantation;

— retrieval and re-deployment (if applicable);

— physiologic loading conditions during and post-implantation.

Residual stresses/strains resulting from manufacturing processes that were not included in test specimens (e.g. material coupons) and any stress concentrations associated with the manufacturing process should be included in the stress/strain analysis. Residual stresses/strains might also result from the device crimping process, loading the device onto an associated delivery system, and deployment/ implantation.

It is important to ensure that the maximum stresses are not underestimated. Device motion and functional configuration are not always symmetric. For this reason, the stress/strain analysis should be performed on entire device/component geometries unless it is demonstrated that the use of a simplified model, e.g. with symmetry conditions is representative of the full analysis.

An accurate constitutive model for each material should be used in any stress/strain analysis, including time-dependent, temperature-dependent and/or nonlinear models as appropriate. Development of constitutive models or evaluation of appropriate constants for existing constitutive models should be justified and based on testing of material that is representative of the actual structural component, including material processing and environmental exposures (e.g. sterilization). The geometry and mechanical properties of simulated implantation sites should be justified and included in the analysis.

Validation of the stress/strain analysis should be performed to demonstrate sufficient confidence in the predicted results. While it is left to the manufacturer to develop and justify such a validation, the validation should include comparison of predicted simulation results against actual experimental measurements from the heart valve repair device.

O.3 Fatigue characterization

O.3.1 General

Fatigue characterization generally falls into four main categories:

a) stress/life (S/N) for use with classical stress/life assessment;

b) strain/life (ε/N) for use with classical strain/life assessment;

c) fatigue crack growth for use in damage tolerance analysis (DTA);

d) component testing for use in demonstrating fatigue resistance.

The manufacturer should determine and justify the most appropriate characterization(s) and assessment approach(es) for the specific material and device design. However, the particular characterization technique should be consistent with the subsequent lifetime assessment approach used. Fatigue characterization of each structural material/component should be performed so that all properties necessary for the fatigue analysis (e.g. endurance limit) are appropriately determined.

Coupon test specimens used to determine material properties should be produced in such a way as to ensure the specimen is representative of the actual material in the device components (e.g. microstructure, crystallinity, density). For example, material properties for nitinol components (e.g. A_f temperature) should be determined. Device components used as test specimens should be representative of actual clinical components (e.g. fabrication methods, defect population). All test specimens should be exposed/pre-conditioned to all of the environments encountered in manufacturing, shipping and clinical use. Stress or strain levels specified for the fatigue characterization should be justified by the manufacturer and should encompass the worst case anticipated stresses or strains experienced by the component *in vivo*; the worst case anticipated stresses or strains experienced by the component should be obtained from the stress/strain analysis (See O.2). Cyclic test rates/frequencies should be justified by the manufacturer, as they are dependent on the type of material used for the structural components of the device. Testing should be performed in an environment that is representative of the physiological environment with respect to its effect on fatigue behaviour (e.g. PBS at 37°C for medical alloys). The mathematical formulations used for fitting the data, other statistical analysis, and extrapolations to predict endurance limits should be specified whenever applicable. The testing should fully represent the range of deployed device configurations and the loading conditions associated within the implantation site. If all possible deployed device configurations are not tested, it will be necessary to conduct an analysis to identify the configuration(s) of the device with the greatest potential for fatigue failure. If other failure modes are observed as a result of fatigue characterization, they should be reported and appropriately evaluated further.

Fatigue testing should be performed in such a manner as to preserve the anticipated *in vivo* failure mechanism. For example, nitinol has been shown to be relatively insensitive to test frequency and environment for fatigue crack growth measurements. If an accelerated protocol is used (e.g. increased test frequency), the manufacturer should justify the appropriateness of the test frequency chosen.

O.3.2 Stress/life (S/N) characterization

Classical S/N characterization is performed by generating failure data at various cyclic stress levels and load ratios to determine the maximum allowable stress for a specified design lifetime.

Testing should be performed at stress levels, including both amplitude and mean values, at least as severe as those predicted by computational analysis (e.g. FEA) under moderate hypertensive pressures and other relevant *in vivo* loading conditions with a safety factor justified by the manufacturer. Test frequency and environment, including test temperature and physiologically representative fluid, should be specified and justified by the manufacturer.

NOTE An endurance limit, as classically defined, might not exist for all materials when exposed to corrosive environments.

O.3.3 Strain/life (ε/N) characterization

While stress has traditionally been the basis for controlling fatigue tests and as a means of monitoring fatigue performance and failure for conventional engineering materials, strain provides a more practical and appropriate means of analysing materials such as nitinol given its superelastic properties. Strain life (ε/N) characterization is performed by generating failure data at various cyclic strain amplitude levels and mean strain levels to determine the maximum allowable strain for a specified design lifetime. In such cases where stress-life characterization for nitinol is preferred, this alternative approach should be justified by the manufacturer.

Testing should span a sufficient range of both amplitude and mean strain conditions to establish and characterize the fatigue response of the material. Strain levels specified for the fatigue characterization should be justified by the manufacturer and should encompass the worst case anticipated stresses or strains experienced by the component *in vivo*. Test frequency and environment, including test temperature and physiologically representative fluid, should be specified and justified by the manufacturer.

NOTE An endurance limit, as classically defined, might not exist for all materials when exposed to corrosive environments.

O.3.4 Fatigue crack growth (da/dN) characterization

Fatigue crack growth testing is used in association with damage tolerance analyses. This analysis employs a fatigue crack growth relation governing crack propagation from inherent flaws in the material/component. Thus, the fracture toughness and fatigue crack growth behaviour relating the rate of crack growth, da/dN, to an appropriate measure of the cycling crack driving force (commonly taken as the cyclic stress intensity factor) are determined for the component material.

Fatigue crack growth testing can be performed on representative test specimens or actual components. In either case, an appropriate measure of the crack driving force should be known. It is often more convenient and common to use more standard fracture specimens whose crack driving force solutions are readily known and available. Because crack growth kinematics depend on the mode of loading (e.g. opening versus shear), testing should also be performed to simulate the anticipated *in vivo* mode of crack growth.

Unless plane strain conditions are ensured for the test specimen, testing should be performed on specimens whose thickness is at least as thick as the actual component. While machined notches may be used to aid and control the formation of a crack, it might be necessary to pre-crack the specimen prior to generating acceptable crack growth and/or toughness data. However, care should be taken in pre-cracking so as not to overload the specimen. For example, for nitinol, overloads might cause large compressive stresses to develop near cracks, resulting in retarded growth and potentially non-

worst case crack growth behaviour. For the same reason, testing should generally be performed under increasing crack driving force to mitigate potential retardation effects.

Testing should span the range of crack driving force from threshold, or minimum anticipated driving force, to near toughness to adequately establish and characterize the fatigue crack growth behaviour of the material. For example, normally nitinol does exhibit threshold behaviour, below which no crack growth occurs. If a threshold is to be used in subsequent damage tolerance analyses, the manufacturer should establish and verify its existence.

O.3.5 Component testing

Fatigue testing of components of the heart valve repair system may be used to demonstrate fatigue lifetimes under conditions that exceed those experienced by the component *in vivo*. Testing should produce stresses or strains that are representative of the worst case anticipated stresses or strains experienced by the component *in vivo* with a fatigue safety factor justified by the manufacturer. Because component testing might only approximate *in vivo* loadings, a validated stress/strain analysis of the component testing might be required to demonstrate that testing is representative of the worst case anticipated *in vivo* loadings.

A clear definition of "failure" should be established and be consistent with respect to the specific failure mode(s) identified by the risk analysis. Samples should be characterized and evaluated for failure prior to, during and after testing. Evaluation and documentation during testing should be performed, at intervals justified by the manufacturer, to distinguish fatigue-induced damage from testing artefacts. Testing artefacts should in no way influence the potential for the test to cause fatigue-induced damage.

O.4 Fatigue lifetime assessment

O.4.1 General

Based on fatigue characterization completed per O.3, a lifetime assessment of the structural components and/or device should be performed to evaluate risks associated with fatigue-related failure modes. While it is left to the discretion of the manufacturer to determine and justify the most appropriate lifetime assessment approach(es) for the specific material and device design, the particular approach should be consistent with the appropriate supporting characterization technique. If a general material fatigue characterization (i.e. ε/N or fatigue crack growth) was developed, it could be used in fatigue lifetime assessments of several failure modes provided the material data are representative of the material and loadings of each particular failure mode. Deterministic or probabilistic approaches may be employed for fatigue lifetime assessments. If fatigue safety factors are reported, the method by which safety factors were computed should be explained.

The lifetime assessment methods (e.g. stress-life assessment, strain-life assessment) should identify and account for the effects of allowable variances such as dimensional tolerances and manufacturing-related defects, material variations (e.g. voids, impurities, material property variations), and assess whether the methodologies for assuring variances are maintained within the manufacturer's justified acceptance criteria.

O.4.2 Stress-life (S/N) assessment

The S/N structural fatigue life is based on the S/N data to determine the predicted lifetime of the repair device at the maximum mean and alternating stresses as determined from the stress analysis. The stress-life assessment should reflect the inherent variability in the fatigue data as well as a measure of confidence in the stress analysis.

O.4.3 Strain-life (ε/N) assessment

The ε/N structural fatigue life is based on the ε/N data to determine the predicted lifetime of the repair device at the maximum mean and alternating strains as determined from the strain analysis. The