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Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

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

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Contents

Page

Foreword

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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 document 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).

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For an explanation of 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 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*.

This second edition cancels and replaces the first edition (ISO 5910:2018), which has been technically revised.

The main changes are as follows:

— requirements in 7.2.2.3 and an informative annex (Annex J) have been added for test platforms;

— requirements and the informative annex on functional performance assessment have been removed;

— fatigue and durability testing have been combined into integrated device assessment in 7.2.4 and Annex M;

— the description of the types of heart valve repair devices, including the added section on robotically-assisted systems, has been moved into Annex B;

— Annex G on hazard and failure modes and Annex R on clinical imaging have been extensively revised;

— pulsatile flow conditions for the paediatric population have been clarified in Annex H;

— Annex I on boundary conditions has been added;

— annexes on physical and material property definitions and material property testing have been removed;

— additional device design evaluation requirements have been included in Annex N;

— additional evaluation considerations for preclinical in vivo evaluations have been included in Annex P.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

1 Scope

1.1 This document specifies an approach for verifying and validating the design and manufacture of a heart valve repair system through risk management. The selection of appropriate verification and 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 end point includes clinical performance and benefits.

1.2 This document defines operational conditions and performance requirements for heart valve repair systems where adequate scientific and/or clinical evidence exists for their justification. It also describes the labels and packaging of the device.

1.3 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).

1.4 This document does not apply to 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 document 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 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

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 information to be supplied by the manufacturer — 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 17664-1, *Processing of health care products — Information to be provided by the medical device manufacturer for the processing of medical devices — Part 1: Critical and semi-critical 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 20417, *Medical devices — Information to be supplied by the manufacturer*

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*

ASTM F1830, *Standard Practice for Selection of Blood for In Vitro Evaluation of Blood Pumps*

3 Terms and definitions

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

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

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
accessory
device-specific tool that is required to assist in the implantation and/or adjustment of the *heart valve repair device* (3.25), excluding the *delivery system* (3.12)

3.2
active comparator
intervention (e.g. transcatheter or surgical valve repair or replacement) generally accepted as the standard of care for the intended valve device indication that can be used as a basis of comparison for the *safety* (3.45) and effectiveness of the *heart valve repair device* (3.25)

3.3
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 investigational medical device and whether anticipated or unanticipated

Note 1 to entry: This definition includes events related to the investigational medical device or the *active comparator* (3.2).

Note 2 to entry: This definition includes events related to the procedures involved.

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

3.4
boundary condition
displacement, force, moment, pressure or constraint acting on an implanted valve repair device and/or surrounding tissue

3.5
cardiac output
CO
stroke volume [i.e. volume of blood pumped by a ventricle during *systolic duration* (3.53)] multiplied by the heart rate

3.6
coating
thin-film material that is applied to an element of a *heart valve repair system* (3.26) to modify its surface physical or chemical properties

3.7
compliance
C
relationship between the change in radius and the change in pressure of a deformable tubular structure (e.g. valve annulus, aorta, conduit), given as

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

where

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 mm;

r_2 is the inner radius at p_2, in mm

Note 1 to entry: Compliance is expressed as a percentage of radial change per 100 mmHg.

3.8
component-joining material
material, such as a suture, adhesive or welding compound, used to assemble the components of a *heart valve repair device* (3.25), thereby becoming part of the implanted device

3.9
cycle
complete sequence in the action of a native or repaired heart valve under pulsatile flow conditions

3.10
cycle rate
beat rate
number of complete *cycles* (3.9) per unit of time

Note 1 to entry: The cycle rate is usually expressed as cycles per minute or beats per minute.

3.11
delivery approach
anatomical access used to deliver the *implant* (3.28) to the *implant site* (3.29) (e.g. transfemoral, transapical, transseptal)

3.12
delivery system
catheter or other system used to deliver, deploy, attach or adjust the device in the *implant site* (3.29)

3.13
design validation
establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.31)

3.14
design verification
establishment by objective evidence that the design output meets the design input requirements

3.15
device embolization
dislodgement from the intended and documented original position to an unintended and nontherapeutic location

3.16
device failure
inability of a device to perform its intended function

3.17
device migration
detectable movement or displacement of the *implant* (3.28) from its original position within the *implant site* (3.29), without *device embolization* (3.15)

3.18
failure mode
mechanism of *device failure* (3.16)

EXAMPLE *Support structure* (3.52) *fracture* (3.22), calcification and prolapse.

3.19
fatigue
process of progressive localized permanent structural change occurring in a material subjected to conditions that produces fluctuating stresses and strains at some point(s) and that can culminate in cracks or complete *fracture* (3.22) after a sufficient number of fluctuations

3.20
follow-up
continued assessment of subjects who have received the *heart valve repair device* (3.25)

3.21
forward flow volume
volume of flow ejected through the repaired heart valve in the forward direction

3.22
fracture
complete separation of any part of the *heart valve repair device* (3.25) that was previously intact

3.23
harm
injury or damage to the health of people, or damage to property or the environment

[SOURCE: ISO/IEC Guide 51:2014, 3.1]

3.24
hazard
potential source of *harm* (3.23)

[SOURCE: ISO/IEC Guide 51:2014, 3.2]

3.25
heart valve repair device
implant (3.28) 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 of heart valve repair devices in Annex B.

3.26
heart valve repair system
set of elements provided to repair the native heart valve, consisting of the *heart valve repair device* (3.25), *delivery system* (3.12), *accessories* (3.1) as applicable, packaging, labelling and instructions

3.27
imaging modality
method used to visualize and assess native anatomy and/or device position, and geometry and/or function

3.28
implant
device placed surgically or non-surgically into the human body and intended to remain in place after the procedure

3.29
implant site
intended location of heart valve repair device (3.25) implantation or deployment

3.30
indication for use
clinical condition of the patient population that the *heart valve repair device* (3.25) is intended to treat or improve

3.31
intended use
use of a product or process according to the specifications, instructions and information provided by the manufacturer

3.32
linearized rate
total number of events divided by the total time under evaluation

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

3.33
loading
process to affix, attach or insert a repair device component onto or into a *delivery system* (3.12)

3.34
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one *cycle* (3.9)

3.35
non-structural dysfunction
abnormality extrinsic to the *heart valve repair device* (3.25) that results in abnormal function of the device or causes clinical symptoms

EXAMPLE Entrapment by *pannus* (3.36), tissue or suture; paravalvular leak; inappropriate sizing or positioning, residual leak or obstruction after implantation and clinically important haemolytic anaemia. This definition excludes infection or thrombosis of the heart valve repair device and intrinsic factors, which cause *structural native valve deterioration* (3.51).

3.36
pannus
ingrowth of tissue onto the *heart valve repair device* (3.25) which can interfere with normal functioning

3.37
pull-out testing
testing for a situation in which the suture or anchoring device remains structurally intact but tears through the tissue in which it is implanted

3.38
reference device
heart valve substitute or *heart valve repair device* (3.25) with known clinical history used for comparative preclinical and clinical evaluations

3.39
regurgitant volume
volume of fluid that flows through a repaired heart valve in the reverse direction during one *cycle* (3.9)

3.40
repositioning
intentional change of *implant* (3.28) position of a partially or fully deployed *heart valve repair device* (3.25) via a surgical or transcatheter technique, possibly requiring full or partial removal or recapturing of the device

3.41
retrieval
removal of a partially or fully deployed *heart valve repair device* (3.25) via a surgical or transcatheter technique

3.42
risk
combination of the probability of occurrence of *harm* (3.23) and the *severity* (3.48) of that harm

[SOURCE: ISO 14971:2019, 3.18]

3.43
risk analysis
systematic use of available information to identify *hazards* (3.24) and to estimate the associated *risks* (3.42)

[SOURCE: ISO 14971:2019, 3.19]

3.44
risk assessment
overall process comprising a *risk analysis* (3.43) and a *risk* (3.42) evaluation

[SOURCE: ISO 14971:2019, 3.20]

3.45
safety
freedom from unacceptable *risk* (3.42)

[SOURCE: ISO 14971:2019, 3.26]

3.46
serious adverse device effect
SADE
adverse effect of the device that has resulted in any of the consequences characteristic of a *serious adverse event* (3.47)

Note 1 to entry: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event.

3.47
serious adverse event
SAE
adverse event (3.3) that leads to any of the following

a) death,

b) serious deterioration in the health of the subject, users or other persons, as defined by one or more of the following:

 1) a life-threatening illness or injury, or

 2) a permanent impairment of a body structure or a body function including chronic diseases, or

 3) in-patient or prolonged hospitalization, or

 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment

3.48
severity
measure of the possible consequences of a *hazard* (3.24)

[SOURCE: ISO 14971:2019, 3.27]

3.49
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after *sterilization* (3.50)

Note 1 to entry: Sterility assurance level is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275]

3.50
sterilization
validated process used to render a 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.

[SOURCE: ISO 11139:2018, 3.277]

3.51
structural native valve dysfunction
structural native valve deterioration
dysfunction or deterioration intrinsic to the native valve, including calcification, leaflet fibrosis, leaflet tear or flail, resulting in stenosis or regurgitation

3.52
support structure
load bearing structural component of a *heart valve repair device* (3.25)

3.53
systolic duration
portion of cardiac *cycle* (3.9) 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* (3.9).

3.54
thromboembolism
embolic event involving a clot(s) that occurs in the absence of infection

Note 1 to entry: Thromboembolism can be manifested by a neurological event or an embolic event to another organ or limb (e.g. ocular, coronary, mesenteric, femoral).

3.55
total product life cycle
period of time over which a product is developed, brought to market and eventually removed from the market

3.56
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* (3.31) environment

[SOURCE: IEC 62366-1:2015, 3.16]

3.57
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

EXAMPLE Incorrect sizing, suboptimal positioning, structural distortion of the device.

Note 1 to entry: An unexpected physiological response of the patient is not by itself considered a use error.

4 Abbreviated terms

For the purposes of this document, the following abbreviated terms apply.

ADE	adverse device effect
AE	adverse event
CMR	cardiac magnetic resonance
CO	cardiac output
CT	computed tomography
CIP	clinical investigation plan
CFD	computational fluid dynamics
DIC	disseminated intravascular coagulation
DPIV	digital particle image velocimetry
DSMB	data safety monitoring board
ECG	electrocardiogram
EOA	effective orifice area
EROA	effective regurgitant orifice area
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FEA	finite element analysis
FWHM	full width at half maximum
GCP	good clinical practice
HIT	heparin-induced thrombocytopenia
ICE	intra cardiac echocardiography
IFU	instructions for use
INR	international normalized ratio
LV	left ventricle, left ventricular
LVAD	left ventricular assist device
MACE	major adverse cardiac events
MAP	mean arterial pressure
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PET	positron emission tomography

PMCF	post-market clinical follow-up
SADE	serious adverse device effect
SAE	serious adverse event
SPECT	single photon emission tomography
SSFP	steady-state free precession
STS-PROM	society of thoracic surgeons predicted risk of mortality
TAVr	transcatheter aortic valve repair
TEE	transoesophageal echocardiography
TMVr	transcatheter mitral valve repair
TTE	transthoracic echocardiography
TTVr	transcatheter tricuspid valve repair

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 implement a risk management process in accordance with ISO 14971, and define and justify a risk management programme, which should be specified in the risk management plan. Annex G provides a heart valve repair system hazard analysis example.

6 Device design

6.1 Intended use and indication for use

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

6.2 Design inputs

6.2.1 General

The design attribute requirements of ISO 14630 shall apply where appropriate.

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 and 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 the left side of the heart — Adult population

Parameter	General condition			
Surrounding medium	Human heart and human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 beat/min to 200 beat/min			
Cardiac output	3 l/min to 15 l/min			
Forward flow volume	25 ml to 100 ml			
Patient condition	**Aortic peak systolic pressure**	**Aortic end diastolic pressure**	**Peak differential pressure across closed valve**[a]	
			ΔP_A	ΔP_M
	mmHg	mmHg	mmHg	mmHg
Normotensive	90 to 139	60 to 89	80 to 114	90 to 139
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

Key

ΔP_A peak differential pressure across closed aortic valve

ΔP_M peak differential pressure across closed mitral valve

[a] Peak differential pressure across closed aortic and mitral valves estimated using the following relationships:

— ΔP_A ≈ pressure associated with dicrotic notch assuming LV pressure is zero ≈ aortic end diastolic pressure + 1/2 (aortic peak systolic pressure – aortic end diastolic pressure);

— ΔP_M is estimated to be equivalent to the aortic peak systolic pressure.

Pressure values were obtained from References [32] and [33]).

Table 2 — Heart valve repair device operational environment for the right side of the heart — Adult population

Parameter	General condition			
Surrounding medium	Human heart and human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 beat/min to 200 beat/min			
Cardiac output	3 l/min to 15 l/min			
Forward flow volume	25 ml to 100 ml			
Patient condition	**Pulmonary artery peak systolic pressure**	**Pulmonary artery end diastolic pressure**	**Peak differential pressure across closed valve**[a]	
			ΔP_P	ΔP_T
	mmHg	mmHg	mmHg	mmHg
Normotensive	18 to 34	8 to 14	13 to 27	18 to 34
Hypotensive	<18	<8	<13	<18
Mild hypertensive	35 to 49	15 to 19	28 to 34	35 to 49

Key

ΔP_P peak differential pressure across closed pulmonary valve

ΔP_T peak differential pressure across closed tricuspid valve

[a] Peak differential pressure across closed pulmonary and tricuspid valves estimated using the following relationships:

— ΔP_P ≈ pressure associated with dicrotic notch assuming RV pressure is zero ≈ pulmonary artery end diastolic pressure + 1/2 (right ventricle peak systolic pressure – pulmonary artery end diastolic pressure);

— ΔP_T is estimated to be equivalent to pulmonary artery peak systolic pressure.

Table 2 *(continued)*

Parameter	General condition			
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

Key

ΔP_P peak differential pressure across closed pulmonary valve

ΔP_T peak differential pressure across closed tricuspid valve

[a] Peak differential pressure across closed pulmonary and tricuspid valves estimated using the following relationships:

— $\Delta P_P \approx$ pressure associated with dicrotic notch assuming RV pressure is zero ≈ pulmonary artery end diastolic pressure + 1/2 (right ventricle peak systolic pressure – pulmonary artery end diastolic pressure);

— ΔP_T is 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 Clause B.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 embolization;

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 minimize 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 required 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 Annexes C, D and 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 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 and 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.

7 Design verification testing and analysis, and design validation

7.1 General requirements

The manufacturer shall perform verification testing to demonstrate that the design of the heart valve repair system 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.

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

The requirements of this document are equally applicable to new or modified heart valve repair systems. For heart valve repair systems with established clinical history that have been evaluated using the previous edition of this document (i.e. ISO 5910:2018), or for systems that were on the market prior to implementation of the previous edition of this document (i.e. ISO 5910:2018), omission or abbreviation of in vitro, preclinical in vivo and clinical evaluations can be appropriate. 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 can 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 test, testing does 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 (e.g. target reliability and confidence based on the risk assessment, expected variability of the test result, specific intent of the test). Additional information regarding sampling and article conditioning shall be included within each test method defined herein, as appropriate.

7.2.2.2 Test conditions

For repair devices, a wide range of potential loading conditions exist (e.g. cyclic loading changes during cardiac cycle, acute and chronic loading changes post repair); the manufacturer shall consider all potential loads and apply appropriate loads during in vitro testing. Variations in device deployed state shall be considered (e.g. off-axis deployment, partial capture of leaflet, partial anchor tissue insertion) 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 preclinical testing and clinical use and refined over the product life cycle of the device. See Annex I for guidance on the identification of boundary conditions for in vitro assessment of heart valve repair systems.

Where simulation of in vivo haemodynamic conditions is applicable to the test method, consideration shall be given to those operational environments given in Tables 1 and 2 for the adult population. In particular, recommended pressure values provided in Tables 3 and 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. 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 the left side of the heart — Adult population

Patient condition	Aortic peak systolic pressure	Aortic end diastolic pressure	Differential pressure across closed valve	
			Aortic	Mitral
	mmHg	mmHg	mmHg	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 the right side of the heart — Adult population

Patient condition	Pulmonary artery peak systolic pressure	Pulmonary artery end diastolic pressure	Differential pressure across closed valve	
			Pulmonary	Tricuspid
	mmHg	mmHg	mmHg	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 Test platforms

Heart valve repair devices interact with the anatomic structures in the heart during implantation and continued function. A variety of test platforms can be necessary to evaluate the heart valve repair system, including those used to evaluate components of the device (e.g. fatigue, durability) and those to evaluate the system in its entirety (e.g. simulated use assessment).

The test platforms used to evaluate the interactions between the heart valve repair device and anatomy shall be representative of the critical aspects of the intended implant site (e.g. material properties, compliance, geometry, anatomical constraints and structures, physiological interactions) for the target patient population, as deemed appropriate by risk assessment.

Examples of these test platforms include whole heart models (e.g. explanted human hearts, animal hearts), explanted valve models that retain appropriate anatomic structures (e.g. chordae, papillary muscles, annular structures) and mock valves (e.g. silicone valves with anatomic structures). Annex J provides examples of native whole heart or explanted valve models relevant to heart valve repair devices.

7.2.2.4 Reporting requirements

The following information shall be reported for each test in either the test protocol or the final report:

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) identification, description and rationale for chosen test platforms and test conditions;

g) pre-specified acceptance criteria, if applicable;

h) verification that appropriate quality assurance standards have been met (e.g. good laboratory practice);

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

j) 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 or 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 ISO 22442-1, ISO 22442-2, ISO 22442-3 and ISO/TR 22442-4.

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; however, the applicability of the literature data to the heart valve repair device shall be justified. 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 can 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 K provides guidance on considerations for device material properties undergoing changes after implantation.

7.2.4 Device durability assessment

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 to evaluate the risks associated with potential structural failure modes. An assessment of the durability of the heart valve repair device shall be performed to demonstrate that the heart valve repair device will maintain structural integrity for a minimum of 400 million cycles (equivalent to 10 years). If labelling includes an explicit statement about an anticipated in vivo device lifetime of lesser than 10 years (e.g. bridge therapy), the labelling claim shall be appropriately justified, and testing shall be performed to the labelled in vivo device lifetime. Refer to Annex M for guidance on conducting a durability assessment of heart valve repair devices.

The assessment shall include bench testing to demonstrate the durability of the heart valve repair device (e.g. wear testing). Testing may be conducted on full devices and/or sub-components of the device, as appropriately justified in the durability assessment. The manufacturer shall provide a justification if it is not feasible or appropriate to conduct in vitro testing of the heart valve repair device, or to test to 400 million cycles (e.g. devices with biological structural components).

If testing is performed, the test 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 and pressure) and should challenge a device in a manner consistent with in vivo loading conditions. Consideration shall be given to anticipated variations in the implanted device configurations. Particular aspects that can affect the anticipated in vivo loading conditions of the heart valve repair device (e.g. tissue ingrowth) shall be taken into account.

7.2.5 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 a rationale for the selected test methods and justify that all corrosion mechanisms and conditions have been considered through testing or theoretical assessments.

7.2.6 Design specific testing

Design specific testing shall be considered to assess functional requirements that are essential to provide a therapeutic benefit and to assess additional failure modes identified by the risk assessment that have not been already addressed. Annex N provides additional considerations for the design evaluation of heart valve repair devices. Consult Annex O for the requirements of design evaluation of delivery systems.

7.2.7 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, ICE) shall be evaluated. In certain cases, the ability to directly visualize the device and delivery system can be more appropriate and shall be evaluated (e.g. surgical implantation).

7.2.8 Simulated use assessment

The ability to permit safe, consistent and accurate implantation of the heart valve repair device within the intended implant site shall be evaluated using a model that simulates the intended use conditions. This assessment shall include all elements of the heart valve repair system required to facilitate delivery, deployment, adjustment, repositioning and retrieval of the device, as applicable. This shall also include the ability to access, advance and retract the delivery system and accessories from the anatomy.

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). The model shall consider anatomical variation in the intended patient population with respect to vasculature and intended implant site, temperature effects, pulsatile flow, etc. These variations shall include conditions that challenge delivery, deployment, adjustment, repositioning and retrieval of the device, as applicable (e.g. maximum flexion of catheters, least amount of support for catheters). The use of clinical imaging modalities shall be considered for simulated use assessment (e.g. fluoroscopy, TEE, TTE, ICE). A justification for critical parameters of the simulated use model(s) shall be provided.

Potential hazards and hazardous situations identified during simulated use testing shall be documented within the risk assessment (e.g. coronary sinus occlusion, ventricular or atrial perforation). Annex G provides a heart valve repair system hazard analysis example, including potential hazards and hazardous situations.

7.2.9 Human factors and usability assessment

Usability assessment shall be conducted as required in accordance with 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. This assessment shall consider using models utilized for simulated use assessment. It is recommended that usability assessment is conducted throughout the design cycle (see Reference [28]).

7.2.10 Device MRI safety

The manufacturer shall evaluate the safety and compatibility of the implant with the use of MRI. ASTM F2052[16], ASTM F2213[20], ASTM F2182[19], ASTM F2119[17] and ASTM F2503[21] contain relevant methods of evaluation.

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 can be justified to accommodate specific heart valve repair device design features and species-specific anatomic differences. Modifications to the anatomical structures in the animal model can 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. Anatomic species differences and use of diseased or non-diseased animal models shall be considered when interpreting results from preclinical in vivo testing. If a determination is made that preclinical in vivo evaluation is not required, a justification shall be documented.

The preclinical in vivo evaluation shall include the following steps.

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 embolization 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) embolization of material from the implant site, delivery system or heart valve repair device;

   6) migration or embolization 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 loading time, maximum number of device manipulations). 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 can 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 or techniques to identical anatomic and physiological conditions as the test device.

g) Perform the evaluation using experienced and knowledgeable test laboratories, under appropriate quality assurance standards (e.g. good laboratory practice).

h) Justify and perform the evaluation 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 in accordance with the parameter(s) under investigation. New devices (e.g. new design or novel blood-contacting materials) require an extended duration of the observation period (not less than 140 days). A minimum duration less than 140 days may be suitable for evaluating minor modifications of an existing heart valve repair device, such as investigations of healing. Any preclinical investigation with a designated end point of less than 140 days requires a justification with rationale as to why a longer survival period was not attempted.

For survival studies, a post-mortem examination shall be performed (e.g. macroscopic, radiographic, histological) focusing on device integrity and delivery system or 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 embolization; 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 l/min to 6 l/min) in the same animal;

g) serious adverse events (e.g. myocardial infarction, significant cardiac arrhythmias, embolization, 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 7.3.3 to meet the requirements of 7.3.2.

The test report shall include:

a) the identification of each of the system components (delivery system, heart valve repair device and accessories) and other auxiliary devices used in the procedure (product description, serial number, and other appropriate identification);

b) a 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) a description of the implantation procedure, including delivery, deployment, sizing technique, device anatomic location, imaging technique(s) and any procedural difficulties;

d) a 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) the 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) an 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;

j) the International Standard used (i.e. ISO 5910:2024);

k) any unusual features observed;

l) the date of the test.

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 delivery system (e.g. robotic assisted delivery), as well as expanded indications for use to investigate those risks and aspects of clinical performance that cannot be fully evaluated from preclinical or other available data. If a determination is made that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided.

For minor modifications to clinically well-documented heart valve repair devices, the manufacturer shall justify omission or abbreviation of clinical investigations.

Clinical studies are recommended for design changes of a marketed device that can affect the safety and effectiveness (e.g. novel blood-contacting materials, changes that alter the flow characteristics or haemodynamics, changes that affect the mechanical loading on the valve repair device). The clinical study design, sample size and end points shall be justified based upon the risk analysis for design changes or device modifications under evaluation.

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. Completeness of the follow-up is essential. 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. Humanitarian use (e.g. compassionate use, emergency use, special access) is a separate process and is not considered part of the clinical programme. A series of patients receiving a novel device under humanitarian 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 the heart valve repair device or system and patient selection prior to initiation of a larger clinical investigation following further preclinical testing.

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 shall include specific inclusion and exclusion criteria, use of accepted end point 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.

Implantation of a new repair device for a previously failed implant (e.g. ring, valve) can require a clinical investigation for the specific indication. For clinical investigations to evaluate a repair of a previously implanted heart valve device, the protocol should be specific regarding the position and dimensions of the failed prosthesis. The protocol should also clearly indicate which types of previously implanted prostheses should be excluded from the investigation.

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 (see 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 can 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 valve disease);

d) the degree of haemodynamic improvement achieved;

e) crucial device specific technical factors involved in implantation;

f) the appropriate selection of available sizes and/or shape configurations;

g) the potential for adverse haemodynamic effect.

7.4.2.2 Data collection and monitoring

7.4.2.2.1 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) should be used where applicable as it can enhance assessment (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 laboratory (Core Lab) 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 References [31] to [33]). Imaging follow-up time points shall be specified and justified, and the follow-up shall be complete as specified in the CIP. The CIP shall be conducted in accordance with ISO 14155 with clearly defined objectives. The CIP shall specify safety and effectiveness end points (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, such as new devices shall at least be non-inferior to standard of care.

Studies should employ measures to minimize bias. 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. For patients who withdraw consent, follow-up ends at the time of the withdrawal.

The manufacturer is responsible for ensuring collection of appropriate information. The study design shall be consistent with the objectives of the CIP. For a given study, the CIP should be standardized. The data collection forms shall be standardized across institutions and investigators. The use of an independent clinical events adjudication committee to classify events against pre-established criteria, and Core Labs are recommended for outcomes that can 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 DSMB or an independent medical reviewer 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 significant modification to well-established device). Study populations shall be representative of the intended post-market patient population, including aetiology and pathology.

7.4.2.2.2 The following considerations apply to pilot phase studies:

a) pilot phase studies are exploratory in nature and do not always 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) patient selection shall involve a heart team approach with at least one non-conflicted physician (according to the criteria of the relevant ethical committees);

c) the consent process shall inform the subjects of the pilot phase nature of the study and alternative options including other approved devices;

d) the limitation on rate of enrolment (e.g. evaluation of acute outcomes after each patient and before treating the next patient);

e) a clinical events committee should be used for adjudication of adverse events;

f) an oversight of the study safety shall be performed by a DSMB or an independent medical reviewer;

g) re-evaluation of risk-benefit profile based upon study outcomes.

7.4.2.2.3 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 end points and duration.

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

a) ethical considerations can 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.

Important differences between surgically implanted and transcatheter devices need to be considered for study design. See Annex B for additional information.

7.4.2.2.5 Explant analysis is a vital part of device evaluation. In the event of subject death, valuable information about implanted devices can be obtained by autopsy, which should be encouraged whenever possible. Devices explanted or obtained at autopsy should be assessed by a cardiovascular pathology core lab. The results of analyses should be reported in accordance with the CIP including operative or autopsy photographs of the device in situ and after explant. 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 inspected for damage (e.g. wear, corrosion) and subjected to appropriate functional, imaging and histopathological investigations.

7.4.3 Study end points

The choice and timing of primary and secondary study end points shall be driven by the study objectives, the disease, the patient population, the technology, the post-procedural treatment (e.g. heart failure medication, antithrombotic medication) and anticipated risks.

End points shall include safety and effectiveness such as time-related valve safety, quality of life, symptomatic and functional status, and device and procedural success. Other tertiary or descriptive end points should be considered relative to the technology.

Further suggestions for clinical investigation end point selection and timing for valve repair devices are provided in Annex S.

7.4.4 Ethical considerations

Although novel valve repair technology can 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 stage 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 can 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. The 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 [34] and [35]). 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 appropriate and in line with ISO 14155, and it shall not be so large as to encourage patients to participate.

See also 7.4.5 for additional detail for site and investigator selection considerations. Ethics committee or institutional review board approval shall be obtained for both pilot phase and pivotal studies.

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 [32], [36] to [39]). Clinical investigations shall be designed to include enough subjects, investigators and institutions to be representative of the intended patient and user populations. The design shall include consideration of and justification for such aspects as disease aetiology, disease severity, gender, age (e.g. adult, paediatric) and other special patient characteristics (e.g. ethnicity) and 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) or Ethics Committee (EC);

   4) qualified centres, following the guidelines on operator and institutional requirements published jointly by the professional societies (see References [25] to [27]);

   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 GCP, including but not limited to: regulatory agency and IRB or 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) avoidance of competing studies (e.g. to avoid selection, channelling biases);

5) minimising potential conflicts 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 [34] and [35]).

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 prospective 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 can 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 (see 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 end points 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).

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. When using devices in niche indications, rare diseases or less common patient populations (e.g. paediatric, adult congenital), smaller sample size and shorter premarket follow-up durations can apply but shall be defined and justified based on disease prevalence, unmet clinical needs and risk-benefit considerations. However, this justification does not apply to any post-market clinical follow-up activities for these devices.

Table 5 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, with probabilities of one-sided type 1 error of 5 % and probability of type 2 error 20 % (power is 80 %), the sample size (in patient-years) is determined to be $9{,}72/R_c$, where R_c is the complication rate currently considered acceptable for similar devices. For example, to detect a complication rate of 2,4 % per year or higher, this would require 9,72/0,024 = 400 patient-years (see References [40] to [42]).

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 indications for use, the outcomes measured, and, if relevant, the type of device modification. The indications for use include the disease and population for which the device is intended, considering the expected duration of survival in such a population without the investigational device and survival in patients treated with conventional care or conventional therapy, including comparable devices.

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. It is recommended that each patient should be presented to a central eligibility committee to evaluate the appropriateness for enrolment.

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 (with or without guideline directed or optimal medical therapy);

e) predicted risk of surgical morbidity or mortality (e.g. STS Score, EuroSCORE II);

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 and 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 and post-procedural anticoagulation or antiplatelet regimens;

k) life expectancy;

l) device or 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.

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), 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) NYHA functional class and relevant STS-PROM score or logistic EuroSCORE II 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 [32], [43] to [46]);

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 or failed prosthesis or repair and to assess implant site and annulus size (see Annex R);

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 and exit time, access site entry and exit time, length of hospital stay);

c) date and 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 and stop, dosage, changes, change justification (e.g. antithrombotic regimen, inotropes);

g) list of all procedural devices (e.g. guidewires, catheters, introducers and dilators, embolic protection devices);

h) list of monitoring devices (e.g. arterial line, pulmonary artery catheter, pulse oximetry);

i) mechanical circulatory assist devices (e.g. 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) including fluoroscopy time and total radiation dosage (see IAEA RS-G-1.5[24]);

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 (e.g. PCI);

n) elements of procedure, including any adjunctive procedures performed (e.g. contrast volume, radiation dosage, 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) implant position (e.g. aortic, mitral, pulmonic, tricuspid) and precise anatomical implant position in relation to surrounding cardiac structures (e.g. leaflets, tissue annulus);

r) assessment of handling, visualization, deployment, repositioning or exchange, including number of re-sheathings and recapturing for proper positioning, orientation, implant location, and insertion and withdrawal of delivery system, where appropriate;

s) procedural complications, including acute interventions (e.g. peripheral vascular intervention, coronary obstruction, acute valve-in-valve, conversion to surgery);

t) evaluation of repaired heart valve function and geometry by echocardiography (e.g. EOA, EROA) 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.

u) blood tests performed post procedure (e.g. full blood count, renal profile, cardiac enzymes).

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 discharge, 30 days, at least one specific time point between three and six 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 can 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, including specific parameters to be reported;

c) NYHA functional class;

d) health-related quality of life indicator(s);

e) functional assessment (e.g. 6 Minute Walk Test peak VO_2);

f) device, valve or adjacent structural assessment (e.g. structural integrity, thrombus deposition) with appropriate imaging (e.g. TEE, TTE, CT); see Annex R; the selection criteria for all patients shall be documented in the CIP;

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 can be indicated;

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

k) cardiovascular medications (e.g. heart failure and antiarrhythmic medications) including start and 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) date and reason for reintervention (e.g. reoperations or conversion to surgery or percutaneous);

o) date and cause of death;

p) explant analysis and autopsy report, if performed; explant analysis shall include histological assessment to document the extent of thrombus and/or fibrous tissue, if present on the device the autopsy report shall include any evidence of organ damage from thromboembolism.

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 received the implant (see Annexes Q, R and S). A justification shall be provided for those who were randomized 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

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, extra-cardiac embolization, adverse effects on cardiac 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.

Further follow-up to 10 years post implant shall be conducted on the pivotal phase cohort with end points 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 is not feasible (e.g. high-risk patients, elderly) and the follow-up duration shall be justified.

Beyond the initial pivotal phase cohort of patients, it can 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 PMCF study and a methodology employed to minimize bias in patient selection.

Follow-up should be as complete as possible, avoiding patient self-reporting, include a clear statement of follow-up 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 pre-market and post-market cohorts shall be analysed and reported separately and in aggregate.

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; remote telemetry (e.g. digital device) may be considered if applicable;

c) follow-up shall include physician examination of the patient wherever possible and any relevant clinical assessments; a structured imaging protocol shall be implemented; the percentage of each follow-up method shall be documented in the final post market follow-up report.

8 Manufacturing verification and validation

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 and 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.

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 can 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 examples of a hazard analysis for a transcatheter repair device. The brainstorming, decision making and 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 the 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 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 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 can 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 or prior preclinical in vivo experience in the same model 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 can 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 document, 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 verifications and/or 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 can 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, 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 end points are contained within several publications[47]-[50]. 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 can 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 can be a relevant parameter for some heart valve repair devices, while some repair devices can 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 can 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

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; refer to IEC 62366-1. Human factors aspects that can 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)

Types and examples of heart valve repair devices and delivery systems

B.1 General

This annex provides types and examples of heart valve repair devices and delivery systems that are intended to improve heart valve function.

B.2 Types of heart valve repair devices

B.2.1 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.

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 is not always possible.

B.2.2 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 can 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 positioning and deployment of the device without complications, including repositioning post deployment and some degree of reduction in regurgitation should 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.

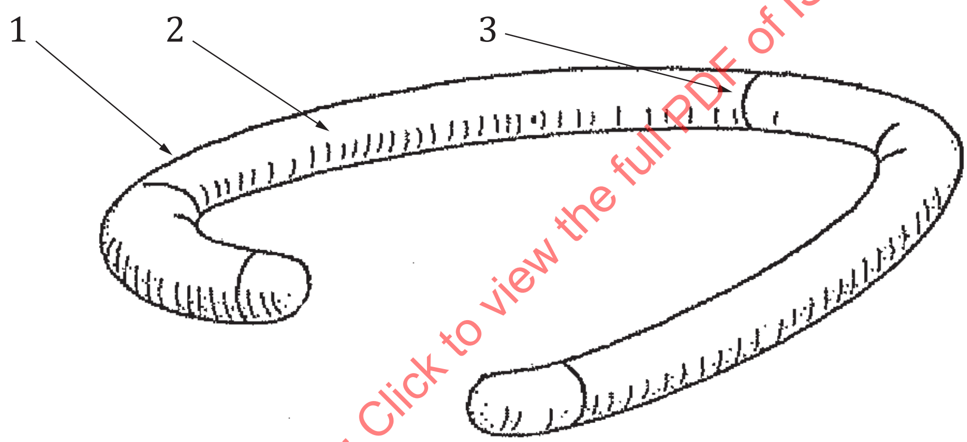
B.2.3 Robotically-assisted systems (robots in interventional cardiology and surgery)

Robotically-assisted heart surgery, also referred to closed-chest heart surgery, is a type of minimally invasive heart surgery performed within a clinical investigation. The procedure utilizes a specially designed robotically assisted system to control surgical instruments during the procedure.

Robotically-assisted surgery has changed the way certain heart operations are being performed. This technology allows surgeons to perform certain types of complex heart surgeries with smaller incisions and precise motion control with loss of tactile feedback. Appropriate risk-benefits must be evaluated and considered during clinical investigation, in conjunction with the end points for the device being studied.

Diagnostic tests should be performed to determine if appropriate candidates are able to undergo robotically-assisted surgery. These can include exams such as an echocardiogram, a CT scan, a chest X-ray, and/or cardiac catheterization to provide more information regarding the condition, anatomy and overall health status.

B.3 Examples of heart valve repair devices



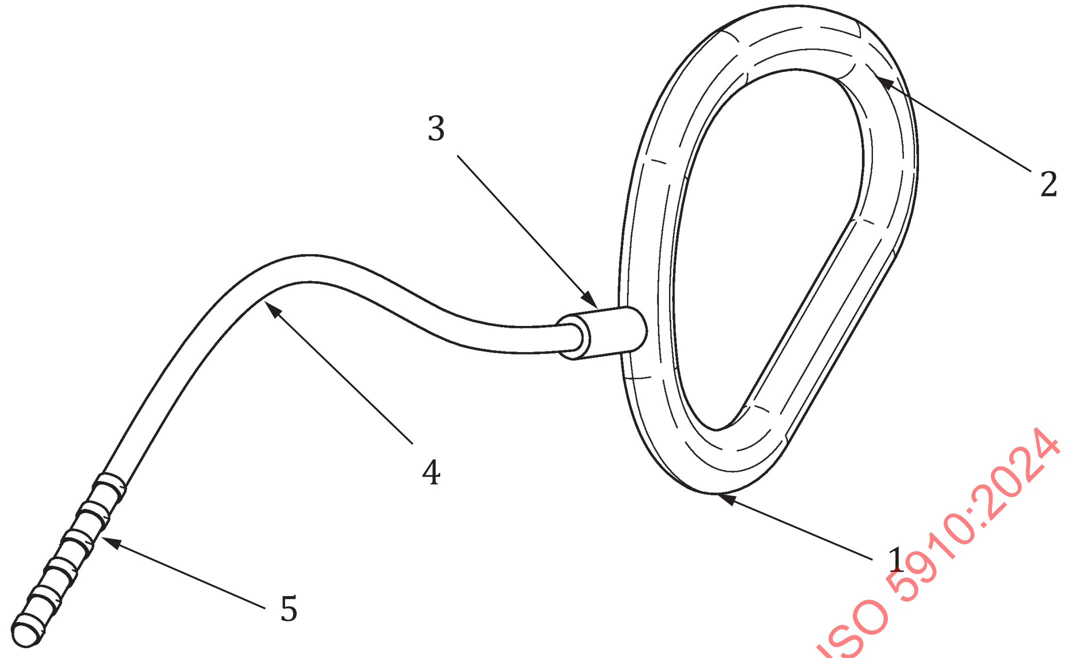
Key

1 covering

2 stiffening element

3 suturing markers

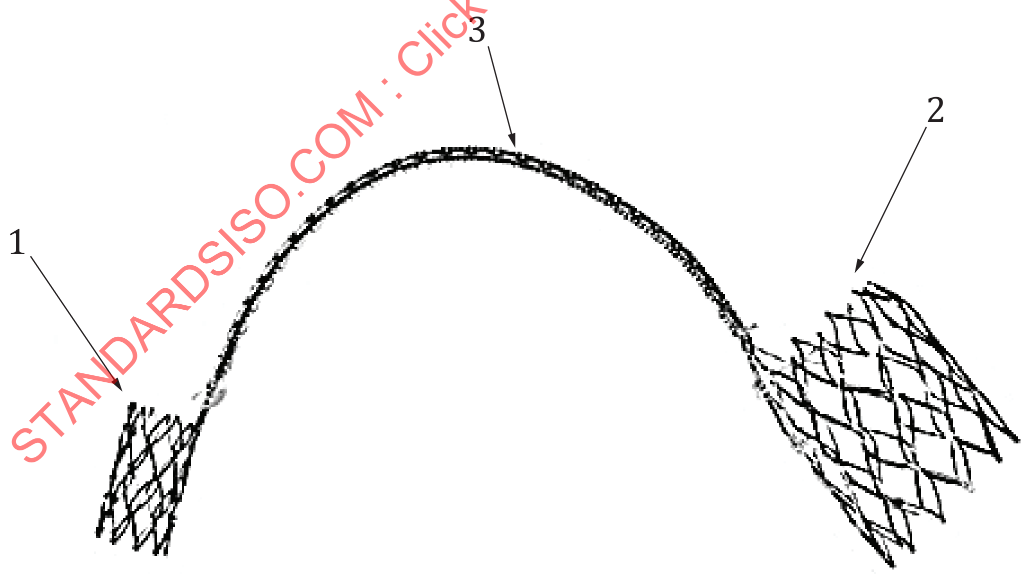
Figure B.1 — Surgical annuloplasty device



Key

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

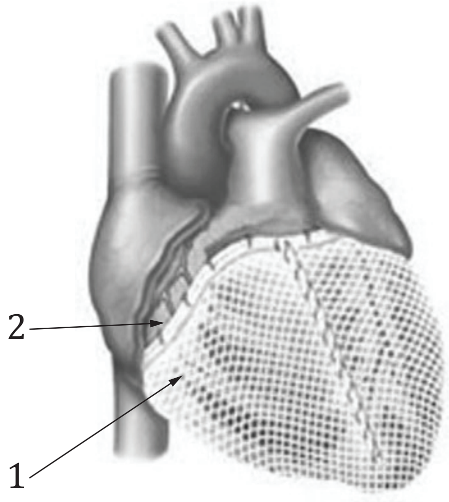
Figure B.2 — Adjustable annuloplasty device



Key

1 distal anchor
2 proximal anchor
3 bridging segment

Figure B.3 — Coronary sinus reshaping device

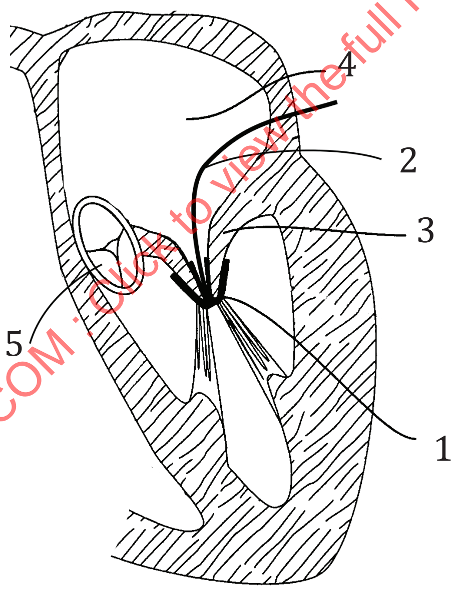


Key

1 compliant external mesh

2 mesh anchors and attachments

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



Key

1 leaflet grasping arms

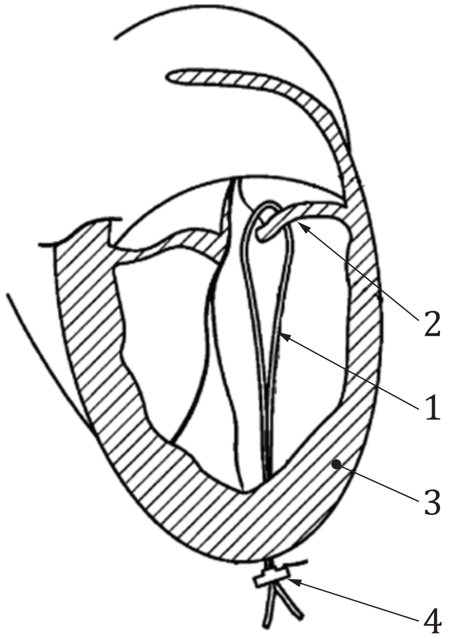
2 device attachment to delivery system

3 native mitral valve leaflets

4 left atrium

5 aortic valve

Figure B.5 — Leaflet edge-to-edge repair device



Key

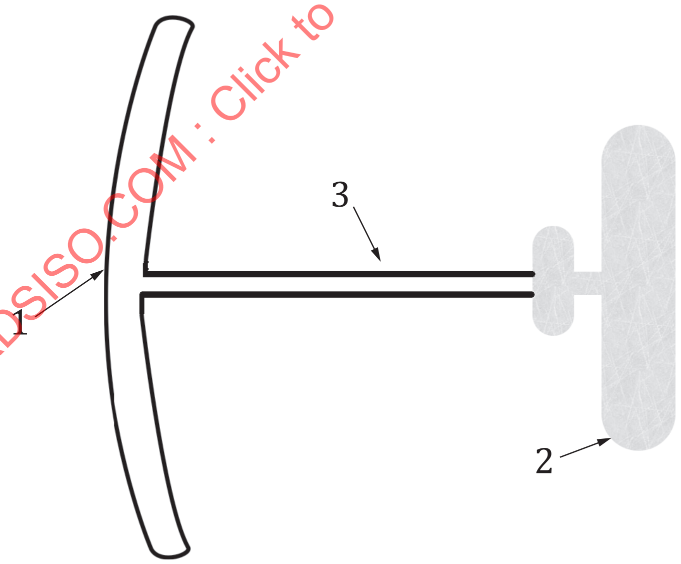
1 synthetic chord

2 valve leaflet

3 ventricular wall

4 chordal attachment to ventricle

Figure B.6 — Artificial chordae device implanted percutaneously



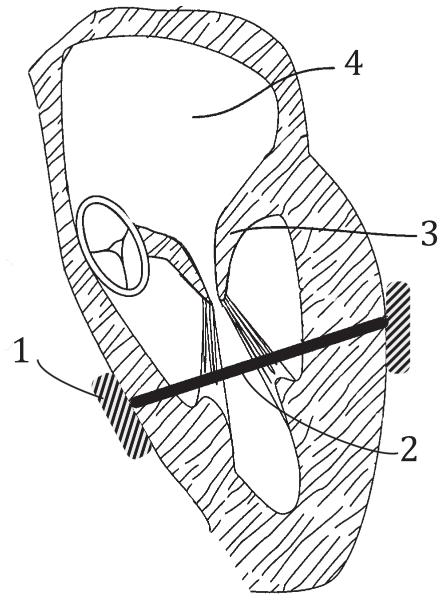
Key

1 coronary sinus anchor

2 septal anchor

3 bridging segment

Figure B.7 — Septal shortening device



Key

1 ventricular pad

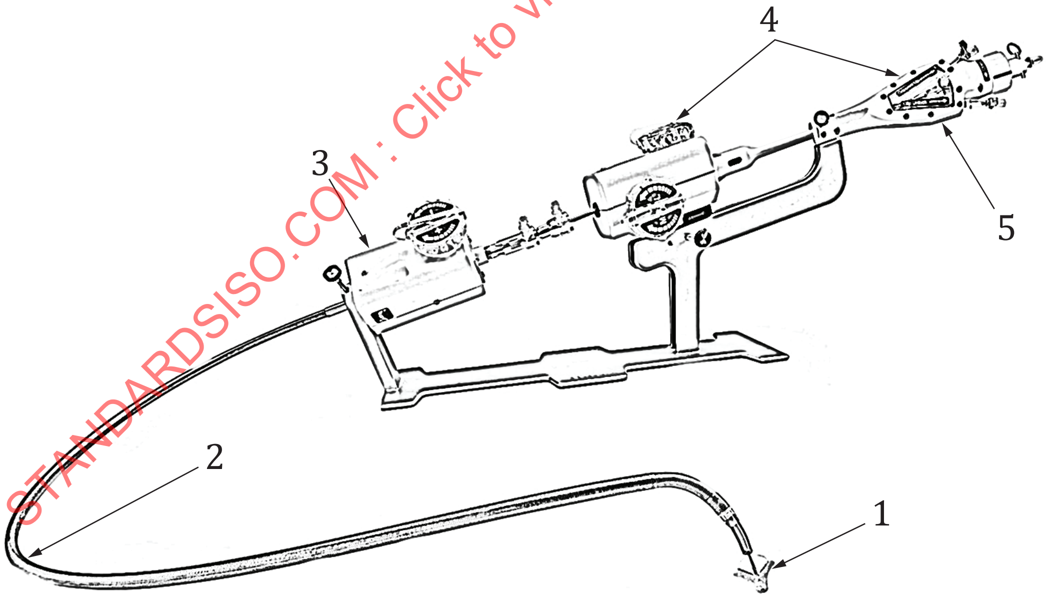
2 bridging element

3 mitral valve leaflets

4 left atrium

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

B.4 Examples of heart valve repair device delivery systems



Key

1 implant

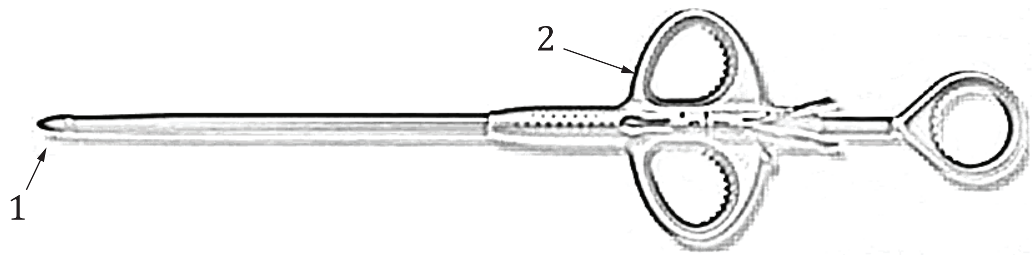
2 steerable guide, steerable sleeve and delivery catheter

3 steerable guide handle

4 implant delivery system

5 delivery catheter handle

Figure B.9 — Delivery system for transcatheter edge-to-edge mitral repair device



Key

1 leaflet capturing jaws

2 operator handle

Figure B.10 — Delivery system for leaflet capturing device

Annex C
(normative)

Packaging

C.1 Requirements

The packaging requirements of ISO 11607-1, ISO 11607-2 and 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, shelf life, transport and handling conditions, unless the package that maintains sterility is damaged or opened. If necessary, based on risk assessment, there shall be a means to show if the packaging was exposed to abnormal conditions (e.g. freezing, excessive heat, container damage) during transit or storage that damaged the heart valve repair system.

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 ISO 11607-2.

C.3.2 Outer container

The unit container(s) shall be packaged in an outer container(s) (sales and 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, ISO 20417, ISO 15223-1 and ISO 15223-2 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 and/or lot number;

— size or 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 can 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 and/or lot number;

— size or 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 can 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/or date of issue;
- 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 or 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 or configuration, and serial and/or lot 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 can 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, ICE 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 model, or other appropriate models (e.g. robotic simulation system);

f) a clinical training programme, including proctored cases;

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

h) methods to minimize the risk to the patient if a device malfunction or procedural complication were to occur and providing training for the same.

Annex E
(normative)

Sterilization

The sterilization requirements of ISO 14630 shall apply, together with this annex.

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 17664-1 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

The characteristics of a heart valve repair device are:

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

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

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

— structural and non-structural materials (e.g. stainless steel, nitinol, titanium, polymer, pericardial tissue);

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

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

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

— the way 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

The characteristics of delivery system are:

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

— delivery tools or catheters;

— guidewire;

— introduction sheath;

— balloon;

— crimping or loading tool;

— access port;

— description of the delivery tools or 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 for the implant or delivery system, including lubricious coatings, primary fixation of tissue, and any anti-calcification, anti-infection or anti-thrombotic treatments should be documented. For device-drug combination products, ISO 12417-1 can apply.

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 References [36] to [39].

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) should be described and their materials of construction should be provided.

Annex G
(informative)

Example of a transcatheter heart valve repair system hazard analysis

It is the responsibility of the manufacturer to establish a comprehensive list of hazards and associated harms for the transcatheter heart valve repair system. The manufacturer should consider both the indicated use and anticipated use of their device (e.g. deployment into a patient with a pacing lead). Table G.1 provides an example for an edge-to-edge repair device that is intended to demonstrate the linkage among potential hazards, foreseeable sequence of events, hazardous situations and harms for transcatheter heart valve repair systems based on the framework provided in ISO 14971. The example shown this annex is not intended to be all inclusive.

Table G.1 — Examples of hazards, associated foreseeable sequence of events, hazardous situations and harms for a transcatheter edge-to-edge repair

Hazard	Foreseeable sequence of events	Hazardous situation	Harm
Leaflet retention element	Insufficient grasping force results in device embolization	Implant travels to unintended location	Coronary blockage resulting in myocardial infarction
	In vivo loads exceed design capability of retention element	Device fatigue failure resulting in component embolization	
Transcatheter procedure	Device implanted in unintended position	Improper leaflet coaptation after deployment	Severe valve regurgitation
	Device deployed without fully capturing target native anatomy	Single leaflet captured	
Delivery system profile	Delivery system profile too large for patient vessel anatomy	Delivery system causes vessel dissection or perforation	Major bleeding
Release knob detachment mechanism	User encounters high frictional force when rotating release knob and implant fails to detach from delivery system	Leaflet damage	Severe regurgitation

Annex H
(informative)

In vitro test guidelines for paediatric devices

H.1 Introduction

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 [52]). The following guidelines for in vitro testing of devices intended for the paediatric population are from a publication based on that workshop[53].

Some definitions of paediatrics include only four groups (newborn, infant, child and adolescent), but input from paediatric clinicians led to adding the “toddler” subpopulation. See Table H.1 for paediatric subpopulation age ranges used in this annex.

Table H.1 — Paediatric subpopulation age ranges

Paediatric subpopulation	Age range *a*
Newborn	0 < *a* < 30 days
Infant	30 days ≤ *a* < 1 year
Toddler	1 year ≤ *a* < 5 years
Child	5 years ≤ *a* < 13 years
Adolescent	13 years ≤ *a* < 22 years

H.2 Pulsatile flow test conditions

Tables H.2, H.3, H.4 and H.5 list pulsatile flow test conditions for pressure difference and regurgitant volume assessments for use with valves in either the left and right sides of the heart. Testing should be conducted to encompass the intended populations and the range of cardiac conditions within each intended population.

Table H.2 — Pulsatile flow test conditions: Left side (pressure difference assessment)

Paediatric subpopulation	Systolic duration %	MAP mmHg	Beat rate beat/min	Simulated cardiac output l/min			
Newborn	50	45	150	0,3	0,5	1,0	1,5
Infant	50	55	120	0,5	1,0	2,0	3,0
Toddler	45	65	100	1,5	3,0	4,0	5,0
Child	40	80	80	2,0	3,0	4,0	5,0
Adolescent	35	100	70	2,0	3,5	5,0	7,0

Table H.3 — Pulsatile flow test conditions: Left side (regurgitant volume assessment)

Paediatric subpopulation	Beat rate beat/min	Systolic duration %	Simulated cardiac output l/min	Mean differential pressure conditions mHg		
Newborn	60	50	1,0	40	80	—
	150	50	1,0	40	80	—
	200	50	1,0	40	80	—
Infant	60	50	2,0	40	80	120
	120	50	2,0	40	80	120
	200	50	2,0	40	80	120
Toddler	60	45	4,0	40	80	120
	100	45	4,0	40	80	120
	160	45	4,0	40	80	120
Child	60	40	4,0	40	100	160
	80	40	4,0	40	100	160
	140	40	4,0	40	100	160
Adolescent	45	35	5,0	40	100	160
	70	35	5,0	40	100	160
	120	35	5,0	40	100	160

Table H.4 — Pulsatile flow test conditions: Right side (pressure difference assessment)

Paediatric subpopulation	Systolic duration %	MAP mmHg	Beat rate beat/min	Simulated cardiac output l/min			
Newborn	50	20	150	0,3	0,5	1,0	1,5
Infant	50	20	120	0,5	1,0	2,0	3,0
Toddler	45	20	100	1,5	3,0	4,0	5,0
Child	40	20	80	2,0	3,0	4,0	5,0
Adolescent	35	20	70	2,0	3,5	5,0	7,0

Table H.5 — Pulsatile flow test conditions: Right side (regurgitant volume assessment)

Paediatric subpopulation	Beat rate beat/min	Systolic duration %	Simulated cardiac output l/min	Mean differential pressure conditions mmHg		
Newborn	60	50	1,0	5	10	20
	150	50	1,0	5	10	20
	200	50	1,0	5	10	20
Infant	60	50	2,0	5	10	20
	120	50	2,0	5	10	20
	200	50	2,0	5	10	20
Toddler	60	45	4,0	5	10	20
	100	45	4,0	5	10	20
	160	45	4,0	5	10	20
Child	60	40	4,0	5	15	30
	80	40	4,0	5	15	30
	140	40	4,0	5	15	30

Table H.5 *(continued)*

Paediatric subpopulation	Beat rate beat/min	Systolic duration %	Simulated cardiac output l/min	Mean differential pressure conditions mmHg		
Adolescent	45	35	5,0	5	20	40
	70	35	5,0	5	20	40
	120	35	5,0	5	20	40

H.3 FEA and life analysis conditions

Tables H.6 and H.7 list conditions for use in FEA and life analysis testing of valves in either the left and right sides of the heart. Analysis should be conducted to encompass the intended populations and the cardiac conditions within each intended population.

Table H.6 — FEA and life analysis conditions: Left side

Paediatric subpopulation	Peak differential pressure mmHg	CO 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 [53] says 15 equivalent years, which comes from US FDA.

Table H.7 — FEA and life analysis conditions: Right side

Paediatric subpopulation	Peak differential pressure mmHg	CO 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 [53] says 15 equivalent years, which comes from US FDA.

Annex I
(informative)

Identification of boundary conditions

I.1 General

Characterization of the target anatomy where a repair device will be placed is fundamental to the understanding of device function, clinical efficacy and safety. It further establishes elements of the risk analysis and boundary conditions used in device functional testing, durability testing (e.g. fatigue, wear, creep), and computational modelling (e.g. FEA, CFD). Anatomy along with biological function (e.g. cardiac pressures, atrial or ventricular muscle contraction) of the target population are translated into boundary conditions used for in vitro bench testing and in silico analysis.

The process of establishing boundary conditions can be viewed in three phases. The initial phase begins with literature reviews, preclinical animal studies and/or bench studies. Any combination of sources may be used to formulate the initial boundary conditions.

As early clinical data are collected, boundary conditions are either confirmed or modified based on the available evidence. Modifications of boundary conditions may be coupled with revisions to relevant animal, cadaver or ex vivo simulated models. Changes in these boundary conditions would then flow downstream to update any in vitro bench testing or in silico analysis. When a larger clinical data sample is collected, the process moves to a final phase where the boundary conditions are further confirmed in a larger patient population sample or revised with new information. The process between the revision and final phase can continue in a loop as more clinical data are collected. This feedback loop is helpful to understanding how variations in the patient population (or subsets) can impact boundary conditions and subsequently device performance and safety.

The purpose of this annex is to provide guidance on key considerations in the establishment of boundary conditions for the testing and analysis of implants. A process to identify boundary conditions for components of the delivery system and procedure is described in Annex O.

I.2 Guidance on the use of published literature

Literature review provides useful guidance on boundary conditions in early phases of device development, before clinical data are available with a new device, however, periodic review of literature can also be helpful to verify boundary conditions at later stages of device development. Published book chapters, peer reviewed journal articles, and conference presentations and/or proceedings may be used to support the definition of boundary conditions for a valve repair device being developed. The use of multiple references is recommended to provide credibility in cited findings and referenced studies should be representative of the target patient population.

In cases where a minimally invasive valve repair device is being developed to mimic a more invasive surgical valve repair procedure, surgical studies may be used to develop boundary conditions with an engineering rationale provided to support their applicability. In cases where a new minimally invasive repair device is similar to a previously approved (predicate) valve repair device, studies performed on predicate(s) may be used to develop boundary conditions with an engineering rationale provided to support their applicability.

When ranges of data are cited to generate boundary conditions, statistical techniques may be applied to calculate worst-case conditions when an appropriate data sample is available. Safety factors or considerations of multiple worst-case conditions may be applied to increase confidence that a worst-case has been determined when sample sizes are limited.

I.3 Animal and human models

Complex interactions between the implant and the surrounding anatomy can require the use of live animal models (i.e. preclinical in vivo testing; refer to Annex P), explanted animal or cadaver organs, or tissue models (i.e. ex vivo testing) to understand boundary conditions used to assess device safety and function. For animal models, explanted hearts may be used in an in vitro bench test, or living animals may be used for an acute or chronic in vivo analysis (preclinical). Refer to Annex P for guidelines on preclinical animal testing.

When determining the boundary condition in any of these models, the analysis does not always require the implantation of the actual device. Depending on the desired measurement, sensors (e.g. load cells, strain gauges) or surrogate devices (e.g. deflectable frame structures) may be used in order to measure in vivo forces or deflections. Computational modelling may additionally be used as a translational tool as described in this clause.

Differences between the animal and the human models must be taken into consideration when used in boundary condition development. Generally, the porcine and ovine models are the most common due to the long history of use in structural valve research, animal availability and ease of animal care. A justification of the appropriateness of the animal model to determine boundary conditions should be included in the analysis. Another consideration is the use of healthy animals versus those with induced structural heart disease (e.g. severed chordae, ventricular dilation caused by induced myocardial infarction, papillary muscle displacem<ent). Analysis should take into consideration the state of the model used (healthy versus diseased) and whether the boundary condition results obtained are representative of the anticipated short-term and/or long-term (chronic) human diseased anatomy or considered worst case.

When appropriately selected for the target patient population, the human model offers the most comprehensive and relevant model for boundary condition development. For the human in vivo analysis of boundary conditions, imaging techniques may be used from baseline patient data or with the device implanted acutely and during long-term follow up (see Clause I.4). In cases where human cadaver tissue is used, the cadaver tissue may provide more accurate representation of anatomical geometry, however the tissue is generally more fragile compared to living tissue and can be more difficult to evaluate in an in vitro bench test. An animal cadaver tissue can be used in lieu of human cadaver tissue provided adequate justification is provided to support that the model used is representative and/or considered worst case. Explants from clinical experience or from existing approved medical therapies that are similar in mechanism of therapy can be useful in understanding potential device interaction with surrounding anatomy in the acute and chronic time frames.

I.4 Imaging techniques for boundary condition assessments

A variety of imaging modalities are used for the assessment and quantification of valvular disease. A list of exemplary cardiac imaging modalities is provided in Table I.1 with notes on resolution. Based on the range of capabilities and limitations associated with each modality, multiple modalities can be useful for the accurate determination of boundary conditions relating to an implanted heart valve repair device.

Table I.1 — Spatial, contrast and temporal resolutions of cardiac imaging methods

	Spatial resolution (FWHM) mm	Contrast resolution	Temporal resolution
CT	0,5 to 0,625	Low to moderate	83 ms to 135 ms
MRI	1 to 2	High	20 ms to 50 ms
Catheter angiography	0,16	Moderate	1 ms to 10 ms
PET	4 to 10[a]	Very high, varies[b]	5 s to 5 min[a]
SPECT	4 to 15[a]	Very high, varies[b]	15 min[d]
Echocardiography	~0,5 to 2[c]	Low to moderate	>200 frames/s (<5 ms)

[a] Depends on resolution versus noise trade-off; higher count studies can be reconstructed with better resolution. Dedicated preclinical systems offer substantially improved resolution (<2 mm).

[b] Varies with specificity of radiotracer.

[c] Intravascular ultrasound scanning can have a spatial resolution of 0,15 mm.

[d] General purpose SPECT systems; Novel dedicated cardiac cameras offer improved temporal resolution on the order of 10 s to 5 min.

SOURCE: Reproduced from Reference [54].

Temporal and spatial resolution are both important for the establishment of boundary conditions when significant device movement or deflection is observed. As shown in Table I.1, various modalities are available with exemplary resolutions and limitations provided, however, the imaging system capabilities and resolution limitations unique to the particular system used during a test or simulated procedure should be considered. Multiple modalities in 2D and/or 3D can be used or combined to determine boundary conditions. Additionally, measurements may be obtained without a device implanted, with a surrogate device implanted, and/or with the evaluated device implanted. In cases where the evaluated device is not implanted, a rationale should be provided to support the appropriateness of the boundary conditions identified.

Measurements of device motion, deflection or deformation should be measured with a carefully selected reference point or from an appropriate reference orientation in order to minimize errors when determining boundary conditions. The presence of an implanted device may create imaging artefacts that limit the ability to accurately measure regions in the direct proximity of the device. In these cases, alternate modalities, multiple modalities or additional methodologies can be useful. If applicable, published imaging guidelines should be referenced as best practices to guide the imaging procedure used for specific valves and or disease states in a manner that maximizes the accuracy of the defined boundary conditions.

I.5 In vitro testing and in silico modelling

I.5.1 General

A variety of in vitro testing and in silico modelling techniques may also be used to establish relevant boundary conditions. These methods need to consider the targeted implant anatomy, including potential disease states, as well as environmental conditions (temperature, fluid viscosity, pH, salinity etc.), and relative motion of and forces applied from surrounding structures.

I.5.2 In vitro testing

In vitro testing can be used to establish boundary conditions when direct clinical measurements are not possible or practical. There are several ways to measure boundary conditions, including the use of simulated beating or steady-state heart models (with appropriate flow loops per literature or prior testing) or through material properties testing (such as force measurements on various types of tissues).

When considering in vitro boundary condition assessments, care should be taken to ensure the test model is clinically representative of the patient population (anticipated regurgitation and pressure gradients, disease states of various tissues, appropriate levels of compliance on various structures, etc.). A justification should be provided when a substitute material is used to represent the disease state, such as fixed or healthy tissue or the use of animal or synthetic tissue. Worst case tissue representatives should be used if applicable. The relevant and appropriate portions of the heart (e.g. leaflets, chordae, papillary muscles) should be included in the model.

There are several limitations that must be considered when using in vitro testing to assess boundary conditions in relation to the target patient anatomies. The test methods are not always able to fully characterize device boundary conditions in all disease states or in chronic conditions (i.e. tissue ingrowth). The development of several models can be needed to fully capture the life of the device. If appropriate materials and test environments (pH, salinity, viscosity, temperature) are not chosen for the model, the boundary conditions can be incorrectly assessed.

I.5.3 Computational modelling

In silico modelling can also be used as a method for assessing boundary conditions in situations where the native tissues and anatomical structures are understood (material properties, dynamic forces, flow rates, etc.). This modelling technique can be used as a translational tool for boundary condition development (e.g. using computational analysis and engineering principles to arrive at forces or loads on the implant). Analytical models, FEA models and/or CFD models may be used to translate observations or measurements obtained from a physical model into more useful measures that can be applied in a test method. For example, known heart chamber pressures, sizes and/or motions may be translated into equivalent reaction forces applied to a device using computational techniques.

When using this method for boundary condition development, it is important to understand any acute versus chronic implant changes to the device. Consideration should also be taken to understand if worst-case assumptions from one location can be applied to a similar location (e.g. mitral versus tricuspid valve locations). Simulation results should be validated by comparison with experimental results.

Annex J
(informative)

Test platforms for in vitro testing

J.1 General

Heart valve repair devices target a variety of anatomic structures associated with native heart valves for therapeutic effect. Given the close interaction of these devices with the native anatomy, it is essential to utilize test platforms that mimic the relevant interactions as closely as possible. A variety of test platforms may be utilized for assessing the function and efficacy of these heart valve repair devices. A brief description of different test platforms is provided in this annex.

It should be noted that many different methods may be utilized to test these platforms and numerous citations exist on the subject. Due to the large variety of repair technologies and the corresponding risks of failure, in vitro test setups are associated with a high degree of individualization. Examples provided are intended to be representative of what can be possible with a test platform type; they are not intended to be a comprehensive listing. The platforms used for in vitro testing should be justified.

J.2 Explanted whole heart or torso models

J.2.1 Description

Whole heart models utilize the entire explanted heart and can include portions of the vasculature and/or torso. Testing in these models may involve animating the explanted heart either actively or passively. Active models rely on the heart muscle itself to contract while passive models utilize an external pumping source to drive fluid through the heart. These models may be used for steady forward flow and steady backflow condition testing. These models contain all relevant cardiac structures, including valve structures, ventricles, atria and vasculature (as appropriate). These models may use cadaveric human hearts or explanted animal hearts most commonly porcine or ovine. See References [55] to [57].

J.2.2 Advantages and disadvantages

Explanted whole heart models are useful when the entire heart anatomy is being studied for repairs involving multiple aspects of the valve (e.g. leaflets, annulus, chordae) muscles or for evaluating aspects of the delivery system. These models are also useful due to their realistic mechanical properties. Active models require fresh hearts with minimal time between explant and testing. This may present logistical concerns and limited windows of testing. The cardiac outputs possible with these models are often limited. While passive models are more accurate in general, the entire motion of the heart is not always entirely representative. For example, passive models that require pressurization of the ventricle do not always accurately represent the relationship between leaflet motion and ventricular wall motion.

J.3 Explanted specific anatomic models

J.3.1 Description

Explanted anatomic models involve excising and testing specific anatomic structures. These may include explanted valve leaflets, chordae, ventricular wall or a sub-set of a full heart. These anatomic structures require mechanical structures to support and manipulate their position and can require external pumping to drive fluid through the model. See References [58] to [62].

J.3.2 Advantages and disadvantages

Explanted anatomic models provide appropriate anatomy, motion and mechanical properties for specific regions of interest. They may allow for the adjustability of the anatomy, and flow and pressure conditions to simulate a wide range of possible test conditions. These models can require technical skill in excising and securing tissue. The testing window possible is typically limited due to degradation of the tissue over time. These models do not always capture all relevant interactions between the repair device and the anatomy.

J.4 Mock valve or heart models

J.4.1 Description

These models can be similar to the above-mentioned models but are made from engineered materials such as silicones, hydrogels, polyurethanes or other artificial materials. These models are intended to mimic the anatomic structures and compliance of the anatomy being tested. See References [63] to [65].

J.4.2 Advantages and disadvantages

Being engineered materials, these models provide the greatest flexibility for investigating different geometries and configurations. Advances have been made to more closely represent the compliance and material properties of native tissue, and patient specific models can be created to represent cases of interest. The models may be more controlled and repeatable than explanted models and provide a much longer testing window for evaluations. The models are faster and easier to setup, with no biosafety concerns making them ideal for testing design iterations. These models may be made of clear materials allowing for better visibility. Model design or manufacturing limitations and materials may restrict attributes that can be mimicked (e.g. native tissue material properties, wall thickness). These should be appropriately considered and justified.

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 M; 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).

Annex L
(informative)

Corrosion assessment

L.1 Rationale

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

Many types of corrosion mechanisms can 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 can require modification 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 [66] for types of corrosion assessment.

L.2 General

The corrosion mechanisms described in Clauses L.3 to L.8 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.

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 can 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[18] and ASTM F746[14]. 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[13]) 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 interface between the sample and the mount.

NOTE See Reference [67] for more information on pitting.

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 the 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 as the material passivity is affected by the specific fabrication processes, generic literature is not always 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 or current, such as described in ASTM F2129[18], ASTM F746[14] 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 is 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[12]. Test methods described in ASTM F3044[22] or equivalent methods can be used or modified, for example, by incorporating the experimental setup described in ASTM F2129[18]. 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[11] or equivalent methods can be used or modified by incorporating the experimental setup described in ASTM F2129[18].

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 [68] for more information on fatigue mechanisms in metals.

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 can be necessary to adequately address the corrosion fatigue mechanisms acting on the device.

ASTM F1801[15] 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 [69] for more information on environmental cracking.

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 can 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.

Annex M
(informative)

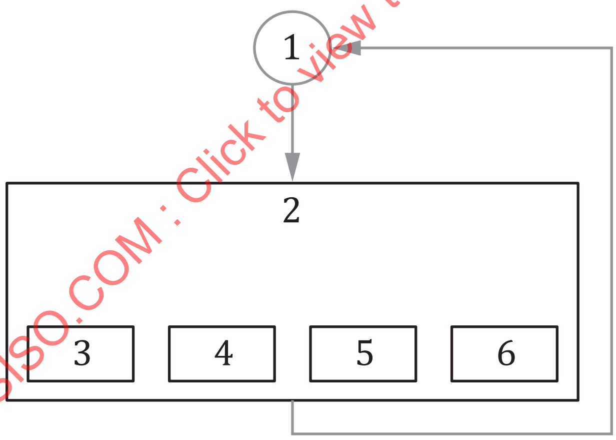
Durability assessment

M.1 Rationale

A heart valve repair device is typically engineered from a variety of materials (e.g. metallic frames, biological tissue, polymer materials, suture) and can include variations in design and deployment methods (e.g. crimping, ballooning) which can affect device durability. These materials or structures may experience a variety of structural failure modes (e.g. creep, fatigue, wear) and each of these modes can require a combination of computational and experimental evaluations to determine their durability over the anticipated device lifetime.

This annex does not address an assessment of the clinical durability of the repair – this should be done through chronic preclinical testing and clinical experience. Refer to Annexes P and S.

A comprehensive risk assessment of structure failure modes of the heart valve repair device is used to identify the components or subcomponents that require durability assessment. These are used to identify experimental or computational approaches to test the durability of the devices. Findings of these tests and models are used along with prior literature and/or testing data and preclinical evaluations to conduct a comprehensive durability assessment of the heart valve repair device, as illustrated in Figure M.1. The conclusions from the durability assessment should be utilized to update the risk assessment as appropriate.



Key

1 risk assessment
2 integrated durability assessment
3 durability testing (e.g. fatigue, wear, creep testing)
4 computational modelling
5 prior literature/ testing data
6 preclinical in vivo evaluation results

Figure M.1 — Durability assessment framework

Prior literature or testing data may be used as appropriate but should be appropriately justified. Considerations for the commonly observed failure modes (creep, wear, fatigue) are presented in this annex. Additional structural failure modes that are identified through risk assessment should be considered as part of the durability assessment.

It is recognized that the same test can be utilized to assess one or more of these structural failure modes. For example, it can be possible to assess both wear and fatigue in the same test; the manufacturer should provide justification as to the applicability of the testing for appropriate failure modes. Similarly, additional failure modes can be observed during testing for a different failure mode (e.g. creep can be observed during wear testing, which can necessitate a supplementary creep test).

M.2 Durability testing

M.2.1 In vivo boundary conditions

Durability assessment should use appropriate in vivo boundary conditions that are representative of the target patient population's anatomic and physiologic loading environment – see Annex I for guidelines on identifying boundary conditions.

M.2.2 Creep

M.2.2.1 General

Creep is a time dependent deformation of a material subjected to either static or time varying stress. Unlike other durability modes, creep can be induced by a static stress being applied to the implant structure. The deformation does not always cause structural damage (i.e. fracture) but may cause degradation changes in the material or mechanical properties of the implant. It is therefore important to understand the potential of creep to affect long-term implant performance and safety.

For certain materials used in heart valve repair devices, in vivo body temperature can be sufficient to cause creep and can vary depending on how the material is manufactured or assembled into the implant (e.g. polymers, composites, biological materials). As identified in the risk assessment, creep testing should be considered for load-bearing structural components composed of these materials that can affect the safety and/or performance of the device or repair.

M.2.2.2 Testing

Materials experience different rates of creep depending on composition and manufacturing processes. Test articles used in creep assessments should therefore be manufactured having the same composition and manufacturing processes as the final implant.

Creep is driven by the degree of stress loading and the temperature at which the load is applied. The higher the load and temperature, the higher will be the rate of creep. Testing should be conducted at relevant temperatures that the device is expected to experience during use, with consideration of environment and time frames of manufacturing, shipping, aging, intraprocedural use and post implantation.

The duration for the evaluation of creep should be justified to be consistent with the anticipated functional life of the polymer or composite component. If an accelerated testing time is used, it should be justified as either representative or represents a worst-case condition.

Polymeric or composite components of the implant subjected to static loads that are important for device safety and function, should include evaluation of mechanical performance over time. Changes in the properties over time should be used to assess the impact on implant performance or safety.

When using fatigue testing to assess creep, the resultant load (in displacement control setups) or the applied load (in force control setups) should be periodically monitored to ensure any creep effects are captured and/or compensated for throughout the fatigue test duration.

M.2.2.3 Computational modelling

Computational stress analysis and accelerated fatigue testing is generally insufficient to address the long-term temperature effect on creep and therefore advanced computational methods can be needed. Advanced computational methods have been developed to predict creep behaviour (e.g. creep continuum damage mechanics, finite element creep methods) and may be used to assess creep risk or to establish a safety factor to ensure that implant deformations due to creep do not impact performance or safety. Computational analysis should be appropriately validated.

M.2.3 Wear

M.2.3.1 General

During the lifetime of a heart valve repair device, wear can occur on various aspects of the device due to forces applied in combination with dynamic motion (e.g. relative motion between components, attachment points of support structures, coaptation bearing surfaces). As such, in vitro testing of the heart valve repair device should be performed to characterize the occurrence and extent of wear, which can lead to excessive structural damage and/or functional impairment. Subclause M.2.3 provides guidelines for evaluating the wear of the heart valve repair device. Consideration should be given to the range of deployment variations, implant deformations and haemodynamic conditions anticipated in vivo. Evaluation of the wear characteristics as part of the durability assessment provides confirmatory data for input into the device risk assessment.

M.2.3.2 Testing

The heart valve repair devices should be tested under appropriate loads or deformations in an appropriate fluid environment to a specified number of cycles required to demonstrate in vitro device durability. Wear testing is typically conducted using accelerated cycle rates – consideration should be given to the effect of test acceleration on the device loading conditions (e.g. load conditions, inertial effects).

Some minor damage is expected on devices after completing wear testing. Failures, however, are characterized by excessive structural damage and/or functional impairment. A clear definition of failure should be established and should be consistent with respect to the specific failure mode(s) identified by the risk analysis. The failure modes to be considered and the pass or fail criteria for the test should be determined based upon the risk assessment. The acceptance criteria should be defined in the protocol prior to execution of the test. Wear testing results should be characterized in terms of the observed damage and the extent of damage. Examples of structural deterioration include holes, tears, gross delamination, abrasion or fraying, fracture, excessive deformation, failure of any individual component, other mechanical breakdown, and/or wear.

M.2.4 Fatigue

M.2.4.1 General

The fatigue assessment provides a relative assessment of the likelihood of structural component fracture during in vivo operation.

There are multiple fatigue approaches that can be utilized for structural components. The manufacturer should determine and justify the most appropriate fatigue characterization assessment approach for each structural component. Stress-life or strain-life approaches are commonly used for heart valve repair device structural components.

A fatigue assessment using a stress-life or strain-life approach (see Figure M.2) consists of:

— the determination of in vivo boundary conditions;

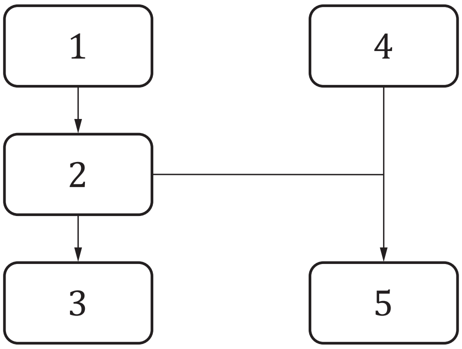
— a validated stress or strain analysis of the structural components under simulated in vivo conditions;

— the material fatigue strength determination;

— the fatigue safety factor or probability of failure determination;

— the component fatigue demonstration testing.

The selection of stress analysis or strain analysis should be chosen based on the material of the structural component.



Key

1 determination of in vivo boundary conditions
2 structural component stress or strain analysis
3 component fatigue demonstration test
4 material fatigue strength determination (*S*-*N* or *ε*-*N* testing)
5 fatigue safety factor or probability of fatigue fracture

Figure M.2 — Example of a structural component fatigue assessment using a stress- or strain-life approach

M.2.4.2 Structural component stress or strain analysis

A validated stress or strain analysis of the structural components should include anchoring mechanisms if applicable. Other valve repair components such as sutures or cloth should be considered for their reaction loads on the structural components.

Quantification of the stress or strain distribution within the structural component(s) is generally accomplished via computational methods such as FEA. Critical inputs to this process are component geometry, mechanical properties (i.e. constitutive model) and the boundary conditions to which the device is subjected. For heart valve repair devices, the analyses should fully represent the range of deployed device geometry and the loading conditions associated with the implantation site (e.g. surrounding anatomical interactions). If all deployed device sizes are not analysed, it is necessary to conduct an analysis to identify the size and deployed device size with the greatest potential for failure.

The stress or strain analysis should account for all physiological loading conditions to which the device is subjected. It is not always 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 native valve opening and closing;

— radial dilatation and compression;

— torsion;

— bending;

— axial tension;

— axial compression;

— linear or 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 normotensive, hypertensive and hypotensive conditions are given in Tables 3 and 4. See Annex H for guidelines regarding suggested test conditions for the paediatric population.

The analyses should consider and establish the effect of in-tolerance variations in the dimensions of components on the magnitude of maximum stress or strain, and consider the effect of in-tolerance variation in material specifications.

The entire stress or strain history of the device in each loading step should be included in the stress/strain analysis, including residual stresses or strains. The entire stress or strain history may include, but is not limited to:

— initial fabrication, expansion, manufacturing, test and inspection;

— crimping or loading onto the delivery system;

— deployment;

— retrieval and re-deployment (if applicable);

— physiological loading conditions during and post-implantation.

It is important to ensure that the maximum stresses are not underestimated. Device motion and functional configuration are not always symmetric. Stress or strain analyses should be performed on the entire valve repair device geometry unless it is demonstrated that the use of a simplified model with symmetry conditions is representative of the full analysis.

An appropriate constitutive model for each material should be used in the stress or strain analysis, including rate-dependent, temperature-dependent and/or nonlinear models as appropriate. Constitutive models should be based on testing of material that is representative of the actual structural component, including material processing and environmental exposures (e.g. sterilization).

If the modelling approach includes simulating the implantation site, the anatomical geometry and mechanical properties should be justified.

Validation of the stress or 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.

M.2.4.3 Material fatigue strength determination

Material fatigue strength testing (stress-life or strain-life testing) is carried out to determine the maximum allowable stress or strain for a specified device lifetime. It can be performed on representative test specimens, actual device components or sections of device components. Test specimens should be representative of the actual material in the structural component (e.g. microstructure, crystallinity, density, transformation temperature), exposed to all of the environments encountered in the device fabrication (e.g. handling, sterilization) and subjected to all preconditioning steps to which the device is subjected during clinical use (e.g. crimping, loading, deployment and recapture of the valve repair device).

Stress or strain levels (e.g. alternating and mean) and test rates or frequencies used for the fatigue strength testing should be justified by the manufacturer. Testing should be performed in an environment that is representative of the physiological environment with respect to its effect on fatigue behaviour. The test should be run to the specified device lifetime without extrapolation.

A justification for use of material fatigue data from the literature should address, but is not limited to:

— material processing, microstructure, composition, surface condition;

— specimen preconditioning, including loading history;

— load ratio, mean and alternating stress or strain ranges used to generate the fatigue data;

— test environment (e.g. temperature, test solution, test frequency);

— sample size used to generate the data;

— test duration represented by the data.

M.2.4.4 Fatigue safety factor or probability of fatigue fracture determination

Variation in fatigue strength can result from manufacturing and material variations (e.g. voids, impurities, material property variations). Variation in the stress or strain can result from component dimensional variation and variation in the in vivo boundary conditions. Residual stresses or strains resulting from manufacturing processes that were not included in test specimens (e.g. material fatigue test coupons) and any stress concentrations associated with the manufacturing process should be included in the stress or strain analysis. Deterministic or probabilistic approaches may be employed for fatigue resistance determinations which account for these variations.

For the deterministic approach, the fatigue safety factor should be computed based on the lower bound material fatigue strength estimate and the upper bound structural component stress or strain estimates. The selection of the lower bound fatigue strength estimate, upper bound estimate for the stress or strain parameters along with the method by which the safety factor is computed should be justified by the manufacturer.

For the probabilistic approach, the distributions of the fatigue strength and the stress or strain should be characterized. The resulting distributions of fatigue strength, and stress or strain should be utilized to compute the likelihood of fatigue fracture using reliability methods (e.g. stress-strength interference modelling).

M.2.4.5 Component fatigue demonstration test

Component fatigue demonstration testing is often carried out under a simplified loading condition as compared to the in vivo boundary conditions to which the component is subjected. Fatigue demonstration testing of the structural components should be conducted under appropriate fatigue loading conditions. Component fatigue demonstration testing is typically accomplished via attribute testing methodologies with sample sizes based upon target reliability and confidence levels. Fatigue-to-fracture approaches (see ASTM F3211[23]) may be used to supplement fatigue demonstration testing. Test rates or frequencies used for the component fatigue testing should be justified by the manufacturer. Testing should be performed in an environment that is representative of the physiological environment with respect to its effect on fatigue behaviour. A clear definition of “failure” should be established prior to testing and be consistent with respect to the specific failure mode(s) identified by the risk analysis.

A stress or strain analysis of the component testing should be performed to demonstrate that testing is representative of the in vivo stress or strain distribution.

After completion of component fatigue testing, specimens should be subjected to detailed inspection for any evidence of notable events (e.g. microcracks in critical fatigue regions, corrosion and fractures).

M.3 Prior literature or testing data

Prior literature or test data may be utilized as part of the durability assessment. A justification for the use of prior literature or test data should address, but is not limited to:

— test specimen manufacturing (including, but not limited to, material processing, microstructure, composition, surface condition, sterilization processes);

— specimen preconditioning, including loading history;

— test environment (e.g. temperature, test solution, test frequency);

— sample size used to generate the data;

— test duration represented by the data.

Data obtained from complaints or reporting databases from real world clinical use of similar heart valve repair systems may also be utilized to inform the durability assessment (e.g. US FDA MAUDE database[76]).

M.4 Preclinical evaluation

Preclinical in vivo evaluations can provide insight into potential durability considerations and boundary conditions for modelling or testing. See Annex P for additional guidance on utilizing preclinical in vivo data.

M.5 Reporting requirements

M.5.1 Durability assessment

The durability assessment report should include:

a) a justification for the durability assessment approach utilized, based on risk assessment;

b) a summary of tests or evaluations utilized for durability assessment;

c) a summary of findings from individual tests or evaluation reports;

d) conclusions related to the clinical impact of durability assessment.

M.5.2 Durability testing

Individual test reports should include:

a) a list of the repair devices and their configurations used to conduct the testing;

b) a rationale and justification for boundary conditions utilized for assessment;

c) a description of test apparatus used;

d) a justification for accelerated test conditions;

e) the pass or fail criteria and justification for the criteria;

f) a description of the fluid used for the assessment, temperature and pH under the simulation conditions;

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

h) 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 or fail criteria.

Annex N
(informative)

Additional device design evaluation considerations

N.1 General

The manufacturer should define all applicable requirements based on the results of the risk assessment for the specific device design. The following additional implant design evaluation requirements may apply as appropriate. The interaction of the device with surrounding anatomic structures should be considered. Both short-term and long-term effects of these interactions on device and repair function should be considered.

The pressure conditions specified in Tables 3 and 4, and other loading conditions should be considered as applicable. See Annex H for guidelines regarding suggested test conditions for the paediatric population.

N.2 Acute anatomic interactions

An assessment of acute anatomical interactions of the transcatheter repair device should be performed to evaluate the risk associated with potential hazards that can be fully or in part, related to the interactions between the device and the native anatomy in the acute phase of the implantation. Hazards can include entanglement, distortion, compression, perforation or tear of anatomical structures. The blocking of structures (e.g. LVOT obstruction, leaflet immobilization, limiting chordal range, coronary compression or occlusion) or the possibility of conduction disturbances should also be considered.

N.3 Chronic anatomic interactions

Changes to the device over time after implantation should be assessed to evaluate the risk associated with the chronic state of the devices. Potential hazards may include chronic interactions that lead to perforation, tear, wear or abrasion, and distortion. If the device performance changes over time, an assessment of the impact of tension or compression forces on the native anatomy should be evaluated. If any native remodelling is possible, the effects of the changes to the native anatomy should be considered.

N.4 Device migration and device embolization resistance

The ability of the implantable device to remain in the target implant site under simulated operating conditions should be assessed. Consideration should be given to variations in the deployed shape, deployed size, implant site characteristics (e.g. degree of annular dilation, amount of prolapse, distribution of calcification, muscular tissue, leaflet or chordal integrity) and device mechanical properties (e.g. compliance). This can include methods such as pull-out testing (e.g. anatomical rupture, loss of anatomical capture, tissue retention), hydrodynamic performance testing (e.g. pulsatile or steady flow testing) or other mechanical testing as appropriate (e.g. radial force, cinching strength).

N.5 Malposition

The manufacturer should determine the optimal deployment location for the device. The impacts of malpositioning or suboptimal placement on the overall therapeutic effects should be assessed based on the device type.

N.6 Implant mechanical forces

For support structures, the manufacturer should characterize the force exerted by the support structure if it directly interacts with the surrounding anatomical structures. Depending on the support structure design, the force can be different in different regions of the support structure and should be evaluated accordingly. In addition, the ability of the support structure to resist anatomic loading should be considered. Examples of such tests are crush resistance, radial resistive force and chronic outward force.

N.7 Environmental degradation

The degradation resistance of all materials (under stress if appropriate) should be determined in a physiological environment. If cyclic loading is present, tests should be conducted under the same type of loading at a frequency that will not mask any possible forms of localized attack. Final forming methods, such as welding, should be considered.

N.8 Calcification

If materials are used where calcification can impact function (i.e. pericardial tissue components), an assessment of the rate and degree of calcification should be considered.

N.9 Effects of device manipulation post implantation

An assessment of the effects of post-implant manipulation on the structural integrity and device function should be conducted if this is an expected use condition to which the device will be exposed.

N.10 Bailout option evaluation

An assessment of the potential bailout options to mitigate any placement, deployment sequence or release causing unexpected results (e.g. embolization, excessive regurgitation) should be conducted.

N.11 Hydrodynamic performance testing

An assessment of the hydrodynamic performance of the implant in simulated native anatomy should be considered. This can help to characterize the effectiveness of the repair by quantifying performance criteria (e.g. forward flow pressure gradients or leakage through the repaired valve). This can include methods such as steady forward flow testing, steady backward flow testing and/or pulsatile flow testing as appropriate.

N.12 Thrombus

An assessment of the thrombogenic and haemolytic potential of the heart valve repair device should be conducted. Methods such as DPIV, CFD and ex vivo methods (e.g. blood loops) can provide a determination of the potential for thrombus formation; however, other methods (e.g. preclinical in vivo evaluation) may also be used as part of this assessment. To perform such an assessment, it is recognized that results from a single method is not always definitive; an integrated approach utilizing a combination of complementary methods can provide the most comprehensive conclusion. The manufacturer should determine and justify the integrated approach and associated characterization techniques utilized for the assessment of the thrombogenic and haemolytic potential based upon the results of the risk analysis. The results of the integrated approach should be interpreted based on comparison to metrics from literature and/or testing of a reference device if appropriate.

N.13 Component interaction (acute or chronic)

Component interactions of the device should be considered. Both short-term and long-term effects of these interactions on device and repair function should be considered. See Annex M for more details on long-term assessments.

N.14 Device alterations during and post delivery

Devices may be crimped, reduced or modified in geometry during delivery into the intended anatomic location – testing should be conducted to demonstrate that the device can deploy and maintain its desired shape or configuration post-delivery after multiple device manipulations or repositions if applicable. Examples of such testing include characterization of implant foreshortening and recoil (for balloon expandable structures).

Annex O
(normative)

Delivery system design evaluation

O.1 General

ISO 25539-1 and ISO 10555-1 were used as a basis for defining delivery system design evaluation requirements specified herein. IEC 62366-1 can also apply. For delivery systems with electrical power, the requirements of IEC 60601-1 can apply. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific delivery system design and delivery approach (e.g. transfemoral, transapical, transseptal, intercostal).

O.2 Implant interactions with delivery system

The manufacturer shall evaluate interactions between the implant and delivery system during use in accordance with the IFU to ensure no damage is induced to implant or delivery system. The following aspects shall be evaluated as applicable:

— crimping or loading of device to delivery system;

— loading device into delivery sheath;

— advancement and tracking;

— positioning and deployment of device within target implant site;

— repositioning or recapturing of device (if applicable) including damage to device or native anatomy;

— withdrawal of delivery system from the patient;

— dimensional compatibility of components with ancillary devices.

O.3 Loading or attachment of device to delivery system

The manufacturer shall define all specific performance parameters to be evaluated to verify consistent and reliable loading or attachment of the device to the delivery system. The manufacturer shall demonstrate that the implantable device can be reliably loaded or attached to the delivery system in accordance with the IFU and satisfy attachment performance requirements such as:

— attachment strength between device and delivery system;

— no damage to device or delivery system;

— loaded or crimped diameter;

— loaded or crimped shape (uniform or non-uniform);

— proper orientation of device into delivery system;

— dislodgement force;

— device sterility;

— device rinsing;

— delivery system flushing (de-airing);

— dimensional compatibility of components with ancillary devices.

O.4 Ability to access and deploy

The manufacturer shall demonstrate that the attachment between device and delivery system shall be sufficient to permit safe, repeatable and reliable delivery of the device to the intended implant site, release of the device from the delivery system and safe removal of the delivery system from the patient in accordance with the IFU. The manufacturer shall define all specific performance parameters to be evaluated to verify safe and reliable deployment of the device within the intended implant site, such as:

— force to deploy (if applicable);

— all relevant forces required to reposition the device (if applicable);

— flexibility and kink resistance;

— bond strength (tensile and torque);

— torquability;

— pushability;

— trackability;

— compatibility with anatomic considerations depending on delivery approach;

— haemostasis;

— particulate generation, including the number and sizes of the particulates generated during implant delivery, deployment, recapture, if applicable, and removal in a simulated use model;

— implant release time, including time of any flow restriction or blockage, time to restore flow and effect on loaded or crimped device;

— dimensional compatibility of components with ancillary devices;

— balloon characteristics (if applicable), which may include inflation and deflation time, relationship between the implant deployment parameters and balloon inflation pressure, mean burst pressure, rated burst pressure and rated fatigue.

Annex P
(informative)

Preclinical ex vivo and in vivo evaluations

P.1 General

Evaluations listed in this annex are not intended as mandatory or all-inclusive. Each of the described evaluations includes minimum parameters necessary to assess a specific issue. However, additional parameters can be relevant depending on specific study goals and/or manufacturer product claims. Acute testing of heart valve repair devices can be performed under non-sterile conditions.

P.2 Preclinical assessment methods

P.2.1 General

Various evaluations should be considered based on the risk assessment. Table P.1 provides examples of evaluations and potential assessment methods.

P.2.2 Ex vivo simulation

Ex vivo simulations refer to benchtop in vitro simulations utilizing cadaveric organs, cadaveric tissue or synthetic models. These simulations can be used to assess handling characteristics of the heart valve repair system including, but not limited to, human factors considerations, repair system preparation, delivery, deployment and interaction with adjacent cardiac structures.

P.2.3 Acute assessment

Acute preclinical assessments refer to intra-procedural and immediate post-procedural assessments used to assess in vivo safety and performance. During these assessments, animals typically remain under general anaesthesia and are not recovered from anaesthesia following completion of the procedure.

P.2.4 Chronic assessment

Chronic preclinical assessments refer to long-term (at least 140 days) studies following the heart valve repair procedure and are used to assess chronic in vivo safety and performance. Investigators may utilize end points shorter in duration than 140 days when applicable. Early-postoperative (e.g. 30 days to 60 days) or late-postoperative (e.g. 90 days) chronic assessment end points may be considered in addition to long-term (at least 140 days) chronic assessment.

Table P.1 — Examples of evaluations

Evaluation	Ex vivo simulation	Acute assessment	Chronic[a] assessment
Haemodynamic performance		X	X
Ease of use (e.g. delivery, deployment, implantation, imaging)	X	X	X
Haematology, clinical pathology		X	X
Device migration and device embolization	X	X	X
Interference with adjacent anatomical structures	X	X	X
Haemolysis (free haemoglobin)		X	X
Thromboembolic complications		X	X
Calcification or mineralization			X
Pannus formation, tissue ingrowth, foreign body response			X
Structural device dysfunction and non-structural dysfunction	X	X	X
Thrombosis: delivery system		X	
Thrombosis: valve repair device			X
Air embolism during implantation procedure (if applicable, based on type of delivery system)	X	X	
Unanticipated delivery system and/or valve repair device-related pathology	X	X	X

[a] Consideration should be given concerning the number of animals enrolled in the chronic study control and test cohorts to ensure that an adequate number of control and test animals (e.g. 1:2 ratio control:test) survive to at least 140 days.

P.3 Evaluations

P.3.1 Haemodynamic performance

Peri-operative imaging should be conducted to document heart valve repair device functionality, anatomic location and alignment, evidence of migration or embolization, and interference with adjacent anatomic structures.

Transvalvular differential pressure (e.g. peak, mean pressure gradient) and regurgitation (if present) should be measured at the time of implantation, serially throughout the duration of the survival study, and on the day of elective euthanasia, across a range of cardiac outputs (e.g. 2,5 l/min to 6 l/min). Transvalvular regurgitation measurement should be performed using a continuous flow measurement technique or other methods which minimize the need to cross the valve with a catheter. Multiple measurements of pressure and flow should be obtained.

Measuring equipment used to assess haemodynamic performance should be described and its performance characteristics documented.

P.3.2 Ease of use

The ease of use should include a descriptive assessment of the handling characteristics of the heart valve repair system (e.g. steerability, trackability, pushability, visibility, ergonomic characteristics, reliability of deployment, ability to recapture and redeploy, if appropriate, procedure duration) and unique features of the system, compared to a reference system (if appropriate). Ancillary procedures (e.g. rapid pacing) should be described. Visualization of repaired valve function and device alignment should be performed intra- or postoperatively using appropriate imaging modalities. The performance characteristics of the selected equipment should be documented.

P.3.3 Device migration or device embolization

Describe and document using imaging or other techniques as appropriate to assess device migration or device embolization.

P.3.4 Interference with or damage to adjacent anatomical structures

Interference with or damage to adjacent anatomic structures (e.g. coronary arteries, coronary sinus, cardiac conduction system, native valve structures, aorta, myocardium) should be assessed and documented as appropriate.

P.3.5 Haemolysis

At a minimum, the following laboratory analyses should be performed: red blood cell count, haematocrit, reticulocyte count, lactate dehydrogenase, haptoglobin and plasma-free haemoglobin. Additional haematology and clinical chemistry analyses should also be conducted to assess inflammatory response, platelet consumption, and liver and renal function.

P.3.6 Thromboembolic events

Thromboemboli should be evaluated in terms of macroscopic description, photographic documentation and a histologic description of the thrombotic material. A full post-mortem exam should be performed to disclose peripheral thromboemboli both macro- and microscopically. Thromboemboli can originate from the access site, implant site, adjacent cardiac chamber, delivery system or heart valve repair device.

P.3.7 Calcification or mineralization

Calcification or mineralization should be evaluated in terms of macroscopic description, photographic and radiographic documentation, and a histological description of any mineral deposits. The results should be compared to those of a control device, if available.

P.3.8 Pannus formation or tissue ingrowth

At a minimum, the distribution and thickness of pannus formation or tissue ingrowth should be described using macroscopic and microscopic methods and photographic documentation. A description of the inflammatory response should also be included in the histologic description.

P.3.9 Structural and non-structural dysfunction

Structural and non-structural dysfunction should be macro- or microscopically documented and described. If deemed appropriate by the programme and/or study director, any unused portion of the explanted heart valve repair device and adjacent structures should be retained in a suitable fixative for additional studies if needed.

P.3.10 Assessment of device and non-device related pathology

The assessment of device or procedure-related and non-device related pathology not otherwise described above should be macroscopically described, histologically evaluated (if appropriate) and photographically documented.

P.3.11 Thrombosis: Delivery system

An evaluation of the acute thrombogenicity of the delivery system with appropriate documentation (e.g. gross and macroscopic photographs) should be conducted at the time of withdrawal of the various delivery system components immediately following the delivery and deployment of the test and a control valve repair device.

It is recommended that the delivery system thrombogenicity should be evaluated orthotopically in the animal blood stream indwelling for a worst-case time (e.g. two times the expected duration of the implantation procedure) with animals maintained at a clinically relevant level of anticoagulation (monitored and documented). It is recommended that the extent of delivery system thrombus formation be assessed along the entire length of the delivery system after an in situ dissection of the vasculature. The delivery system should subsequently be removed, the lumen flushed (e.g. twice the luminal volume) and the extent of thrombus inside the lumen assessed.