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Cardiovascular implants — Cardiac valve prostheses —

Part 3: Heart valve substitutes implanted by transcatheter techniques

Implants cardiovasculaires — Prothèses valvulaires —

Partie 3: Valves cardiaques de substitution implantées par des techniques transcathéter

Reference number
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Foreword

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

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

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

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

For an explanation 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 Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 285, *Non-active surgical implants,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 5840-3:2013), which has been technically revised.

The main changes compared to the previous edition are as follows: the engineering and clinical requirements in the ISO 5840 series have been updated to current specifications and integrated and harmonized across all parts.

A list of all parts in the ISO 5840 series can be found on the ISO website.

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.

Introduction

This document has been prepared for transcatheter heart valve substitutes with emphasis on providing guidance for *in vitro* testing, preclinical *in vivo* and clinical evaluations, reporting of all *in vitro*, preclinical *in vivo*, and clinical evaluations and labelling and packaging of the device. This process is intended to clarify the required procedures prior to market release and to enable prompt identification and management of any subsequent issues.

This document is used in conjunction with ISO 5840-1 and ISO 5840-2.

Cardiovascular implants — Cardiac valve prostheses —

Part 3: Heart valve substitutes implanted by transcatheter techniques

1 Scope

This document is applicable to all devices intended for implantation as a transcatheter heart valve substitute.

This document is applicable to transcatheter heart valve substitutes and to the accessory devices, packaging and labelling required for their implantation and for determining the appropriate size of heart valve substitute to be implanted.

This document establishes an approach for verifying/validating the design and manufacture of a transcatheter heart valve substitute through risk management. The selection of appropriate verification/validation tests and methods are to be derived from the risk assessment. The tests can include those to assess the physical, chemical, biological and mechanical properties of heart valve substitutes and of their materials and components. The tests can also include those for preclinical *in vivo* evaluation and clinical evaluation of the finished heart valve substitute.

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

This document includes considerations for implantation of a transcatheter heart valve substitute inside a pre-existing prosthetic device (e.g. valve-in-valve and valve-in-ring configurations).

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 5840-1:2021, *Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements*

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

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

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

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

IEC 62366 (all parts), *Medical devices — Application of usability engineering to medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 5840-1:2021 and the following apply.

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

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

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

3.1
acute assessment
intra-procedural and immediate post-procedural results used to assess *in vivo* safety and performance

Note 1 to entry: All animals entered into acute, short-term assessment will remain under general anaesthesia for the duration of the study.

3.2
chronic assessment
long-term results following the procedure used to assess chronic *in vivo* safety and performance after the animal has recovered from anaesthesia

Note 1 to entry: The endpoints and durations of these studies should be determined by risk analysis.

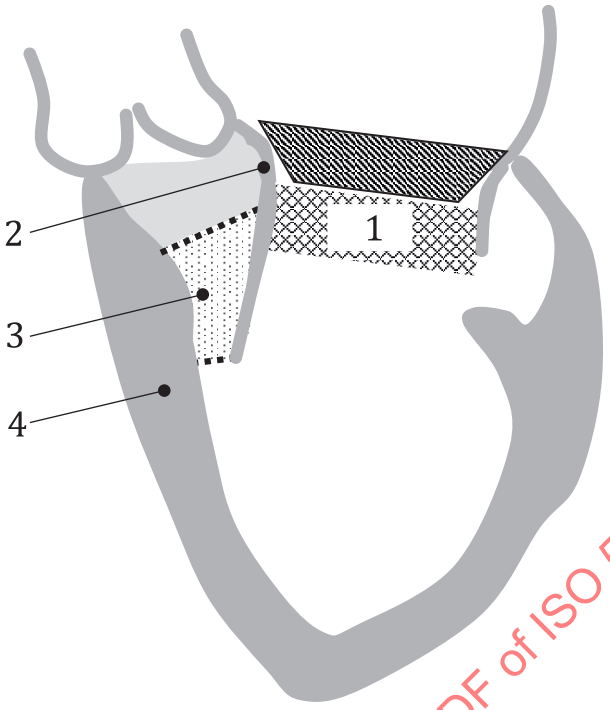
3.3
delivery approach
anatomical access used to deliver the implant to the implant site (e.g. transfemoral, transapical, transseptal)

3.4
delivery system
catheter or other system used to deliver the implant to the implant site

3.5
device migration
detectable movement or displacement of the heart valve substitute from its original position within the implant position and without device embolization

3.6
loading
crimping
process to affix or attach a transcatheter heart valve substitute onto a delivery device and collapse the valve (i.e. reduce its diameter) for insertion via the *delivery system* (3.4) (e.g. catheter), performed either during manufacture or in the clinic

3.7
neo-LVOT
neo-left ventricular outflow tract
region between native anterior mitral leaflet/ transcatheter mitral valve implantation (TMVI) and septal wall, proximal to the aortic valve (see Figure 1)

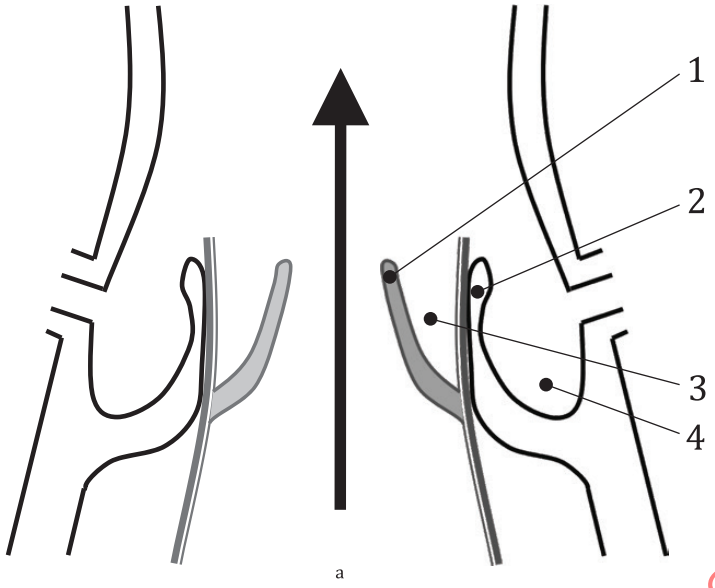


Key

1 TMVI
2 native anterior mitral leaflet
3 neo-LVOT
4 septal wall

Figure 1 — Neo-LVOT formation behind a mitral leaflet

3.8
neo-sinus
region between implanted transcatheter aortic valve leaflet and native aortic leaflet/leaflet of existing bioprosthetic valve (see Figure 2)



Key

1 transcatheter aortic valve implantation (TAVI) leaflet
2 native leaflet
3 neo-sinus
4 native sinus
a The arrow indicates the direction of the forward flow.

Figure 2 — Neo-sinus formation behind an aortic leaflet

3.9
repositioning
change in implant position of a partially- or fully-deployed transcatheter heart valve substitute via a transcatheter technique, possibly requiring full or partial recapturing of the device

3.10
retrieval
removal of a partially- or fully-deployed transcatheter heart valve substitute via a transcatheter technique

3.11
transcatheter heart valve system
implantable transcatheter device, *delivery system* (3.4), accessories, packaging, labels and instructions for use

3.12
valve-in-ring
implantation of a transcatheter heart valve substitute into a pre-existing annuloplasty ring

3.13
valve-in-valve
implantation of a transcatheter heart valve substitute into a pre-existing heart valve substitute

4 Abbreviations

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

AE	adverse event
AWT	accelerated wear testing
CIP	clinical investigation plan
COF	chronic outward force
CT	computed tomography
ECG	electrocardiogram
EOA	effective orifice area
IFU	instructions for use
LA	left atrium
LAA	left atrial appendage
LV	left ventricle, left ventricular
LVOT	left ventricular outflow tract
MRI	magnetic resonance imaging
MR	mitral regurgitation
PMCF	post-market clinical follow-up
PVL	paravalvular leakage
RMS	root mean square
SAE	serious adverse event
TAVI	transcatheter aortic valve implantation [also known as transcatheter aortic valve replacement (TAVR)]
TEE	transoesophageal echo
TMVI	transcatheter mitral valve implantation [also known as transcatheter mitral valve replacement (TMVR)]
TTE	transthoracic echo
ViV	valve-in-valve
ViR	valve-in-ring

5 Fundamental requirements

See ISO 5840-1:2021, Clause 5.

6 Device description

6.1 General

See ISO 5840-1:2021, 6.1.

6.2 Intended use

See ISO 5840-1:2021, 6.2.

6.3 Design inputs

6.3.1 Operational specifications

See ISO 5840-1:2021, 6.3.1.

6.3.2 Performance specifications

6.3.2.1 General

See ISO 5840-1:2021, 6.3.2 for general requirements. Specific transcatheter system requirements are listed in 6.3.2.2 to 6.3.2.4. See Reference [18] for information relevant to TMVI.

6.3.2.2 Transcatheter heart valve system

The design attributes to meet the intended performance of the transcatheter heart valve system shall take into account at least the following:

a) the visibility of the transcatheter heart valve system under fluoroscopy or other imaging modalities;

b) the deliverability and implantability in the target population.

6.3.2.3 Implantable device

The intended performance of the transcatheter heart valve substitute shall include, but not be limited to the following:

a) the ability to be consistently, accurately and safely loaded onto the delivery system;

b) the ability to be consistently, accurately and safely deployed;

c) the ability to be safely retrieved and/or repositioned (if applicable);

d) the ability to ensure effective fixation or anchoring within the implant site;

e) the ability to maintain structural and functional integrity throughout the anticipated lifetime of the device;

f) the ability to conform or interact with anatomical structures within the implant site (e.g. in the aortic position, there is potential for interaction with the coronary ostia, the anterior mitral leaflet and the conduction system; in the mitral position, there is potential for interaction with the aortic root, LA, LAA, LVOT and the subvalvular apparatus);

g) the ability to conform or interact with previously implanted device (e.g. surgical valve, annuloplasty ring, transcatheter valve, valve docking device), if applicable;

h) the ability to allow forward flow with an acceptably small mean pressure difference in all anticipated configurations;

i) the ability to prevent retrograde flow with acceptably small regurgitation, including paravalvular leakage;

j) the ability to resist migration and embolization;

k) the ability to avoid haemolysis;

l) the ability to resist thrombus formation;

m) biocompatibility;

n) the ability to maintain its functionality and sterility for a reasonable shelf life prior to implantation;

o) reproducibility of function.

6.3.2.4 Delivery system

In addition to the requirements in Annex D, the design attributes to meet the intended performance of the delivery system shall include, but are not limited to, the following:

a) the ability to permit consistent, accurate and safe access, delivery, placement and deployment of the transcatheter heart valve substitute to the intended implant site;

b) the ability to permit consistent and safe withdrawal;

c) the ability to resist haemolysis;

d) the ability to resist thrombus formation;

e) the ability to resist blood loss (haemostasis);

f) the ability to recapture, retrieve, reposition and/or remove the transcatheter heart valve substitute (if applicable);

g) the ability to resist particulate generation.

6.3.3 Implant procedure

See ISO 5840-1:2021, 6.3.3.

6.3.4 Packaging, labelling and sterilization

See ISO 5840-1:2021, 6.3.4.

The manufacturer shall provide information and guidance (e.g. imaging modalities and sizing procedure) in the labelling to allow for appropriate preparation of the implant site (e.g. balloon valvuloplasty), selection of appropriate implant size and implantation of the transcatheter heart valve substitute. The manufacturer shall also provide MRI compatibility information in the labelling.

Annex A contains a list of terms that may be used in describing transcatheter heart valve system components.

6.4 Design outputs

See ISO 5840-1:2021, 6.4. See Reference [18] for information relevant to TMVI.

6.5 Design transfer (manufacturing verification/validation)

See ISO 5840-1:2021, 6.5.

6.6 Risk management

See ISO 5840-1:2021, 6.6.

Annex B contains a hazard analysis example specific to transcatheter heart valve substitutes that can serve as the basis for a risk analysis.

7 Design verification and validation

7.1 General requirements

In vitro assessment shall be used to mitigate the risks identified in the risk analysis. General requirements that are applicable to all heart valve systems are provided in ISO 5840-1:2021,7.1. Specific considerations for transcatheter heart valve substitutes are provided in this document. See Reference [18] for information relevant to TMVI.

7.2 *In vitro* assessment

7.2.1 General

The requirements shall be as specified in ISO 5840-1:2021, 7.2.

7.2.2 Test conditions, sample selection and reporting requirements

The requirements shall be as specified in ISO 5840-1:2021, 7.2.2.

For transcatheter valves, the steps of crimping or loading the implant into/onto a delivery catheter and tracking through simulated delivery pathways shall be followed in accordance with the IFU. The implant shall be maintained in the crimped configuration for a duration that mimics the worst-case expected clinical procedure time. If retrieval and repositioning is indicated for the implant in the IFU, the maximum allowable number of re-sheathing/recapturing and deployment cycles specified shall be simulated. Any deviations of the test articles from the finished device shall be justified. The test articles selected shall fully represent the total size range of the implant, the delivery system and accessories.

7.2.3 Material property assessment

7.2.3.1 General

The requirements shall be as specified in ISO 5840-1:2021, 7.2.3.

7.2.3.2 Biological safety

The requirements shall be as specified in ISO 5840-1:2021, 7.2.3.2.

7.2.3.3 Material and mechanical property testing

The requirements shall be as specified in ISO 5840-1:2021, 7.2.3.3.

For ViV and ViR indications, consideration shall be given to the material properties of the existing prosthesis, including bioprosthetic valve leaflet calcification, and their interactions with the materials of the transcatheter heart valve system.

7.2.4 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid dynamic performance of the transcatheter heart valve substitute. The implant shall be deployed using the loading and deployment steps in accordance with the product specification and appropriately placed into the test chamber to simulate the device placement at the intended implant site. The device shall be inspected after loading, recapturing and/or deployment prior to fixturing and testing. ISO 5840-1:2021, Annex I provides guidelines for conducting and reporting steady-flow hydrodynamic tests. Guidelines for conducting and reporting of pulsatile hydrodynamic tests are provided in Annex C. For pulsatile flow testing, the performance of the pulse duplicator shall be characterized. See C.2.3.2 for guidelines related to pulse duplicator characterization. The measurement accuracy and repeatability of the test system(s) shall be evaluated and documented. The hydrodynamic waveforms produced by the pulse

duplicator shall reasonably simulate physiological conditions. Representative waveforms used to generate hydrodynamic test results shall be documented in the test report. Reference [27] provides characteristics of reasonable aortic and mitral waveforms.

For transcatheter aortic valve substitutes, testing shall be performed to compare the hydrodynamic performance of the device to the minimum performance requirements provided in Table 1. Guidelines for designing test fixtures and test parameters are provided in Annex C and C.2.4. Testing shall be carried out on at least three transcatheter heart valve substitutes of each size in each configuration using requirements defined in Table C.2. The minimum performance requirements in Table 1 are provided as a function of deployed valve diameter within implant site (in mm). In addition, testing at challenge conditions shall also be considered to evaluate the device performance over a range of anticipated implant configurations (see Annex C and C.2.4.4 for examples of challenge conditions for transcatheter aortic valve substitutes).

For transcatheter mitral valve substitutes, testing shall be performed to compare the hydrodynamic performance of the device to the minimum performance requirements provided in Table 2. Guidelines for designing test fixtures and test parameters are provided in Annex C and C.2.5. Testing shall be carried out on at least three transcatheter heart valve substitutes of each size in each configuration using requirements defined in Table C.3. The minimum performance requirements in Table 2 are provided as a function of area-derived valve diameter (in mm).

For ViV and ViR indications, hydrodynamic testing shall be conducted in representative configurations of the pre-existing prosthetic devices to compare the device hydrodynamic performance to the minimum performance requirements provided in Tables 1 and 2.

The minimum performance values contained in Tables 1 and 2 reflect requirements against which heart valves substitutes under test shall be evaluated. If a device does not meet these minimum performance requirements, acceptability of the *in vitro* test results shall be justified by the manufacturer.

The minimum *in vitro* performance requirements in Tables 1 and 2 correspond to the following nominal pulsatile flow conditions: beat rate = 70 cycles/min, simulated cardiac output = 5,0 l/min, and systolic duration = 35 % at normotensive conditions, as specified in ISO 5840-1:2021, Table 3 or Table 4. These pulsatile flow conditions are based on a healthy normal adult and might not be applicable for paediatric device evaluation (see ISO 5840-1:2021, Annex E for paediatric parameters).

Table 1 — Minimum *in vitro* hydrodynamic device performance requirements, aortic

Parameter	Deployed valve diameter within implant site mm							
	17	19	21	23	25	27	29	31
EOA (cm^2) greater than or equal to	0,70	0,85	1,05	1,25	1,45	1,70	1,95	2,25
Regurgitant fraction (% of forward flow volume) less than or equal to[a]	20							
[a] For *in vitro* testing, regurgitant fraction includes closing volume, transvalvular leakage and paravalvular leakage volume.								

Table 2 — Minimum *in vitro* hydrodynamic device performance requirements, mitral

Parameter	Deployed area-derived valve diameter within implant site mm					
	23	25	27	29	31	≥33
EOA (cm^2) greater than or equal to[a]	1,05	1,25	1,45	1,65	1,90	2,15
Regurgitant fraction (% of forward flow volume) less than or equal to[b]	20					
[a] For measured mean pressure gradients ≤2 mmHg, computing of EOA is not required.						
[b] For *in vitro* testing, regurgitant fraction includes closing volume, transvalvular leakage and paravalvular leakage volume.						

For transcatheter pulmonary and tricuspid valve substitutes and paediatric devices, minimum performance requirements are not provided in this document; however, the manufacturer shall justify

the acceptability of hydrodynamic performance of the devices. The test chamber shall be representative of the critical aspects of the target implant site (e.g. compliance, geometry, native valve or pre-existing prosthetic device) for the target patient population.

For all transcatheter valve substitutes, additional hydrodynamic characterization testing shall be conducted over a range of test conditions as described in Annex C and C.2.6.

7.2.5 Structural performance assessment

7.2.5.1 General

The requirements shall be as specified in ISO 5840-1:2021, 7.2.5.

7.2.5.2 Implant durability assessment

The requirements shall be as specified in ISO 5840-1:2021, 7.2.5.2.

For ViV and ViR indications, testing shall be conducted in devices that are representative of the anticipated range of configurations.

7.2.5.3 Device structural component fatigue assessment

See ISO 5840-1:2021, 7.2.5.3.

7.2.5.4 Component corrosion assessment

See ISO 5840-1:2021, 7.2.5.4.

For ViV and ViR indications, the manufacturer shall consider all interactions with the pre-existing device in terms of corrosion potential (e.g. galvanic corrosion, fretting corrosion).

7.2.6 Design- or procedure-specific testing

7.2.6.1 General

The following design evaluation requirements shall apply as appropriate. Justification shall be provided for those requirements that are deemed not applicable to a particular design. Additional design evaluation requirements might be applicable as per ISO 25539-1. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific device design. See Annex E for examples of design specific evaluation requirements to be considered.

7.2.6.2 Device migration resistance

The ability of the implanted device to remain in the target implant site (e.g. native valve or pre-existing prosthesis) shall be assessed under simulated operating conditions. Consideration shall be given to variation in deployed shape, deployed size as prescribed in the product specification, implanted depth, implant site characteristics (e.g. native valve, degree and distribution of calcification) and mechanical properties (e.g. compliance) along with consideration for surrounding anatomical structures (e.g. native leaflets, LVOT). For ViV and ViR indications, the manufacturer shall consider simulated operating conditions of the existing device and all interactions with the existing device in terms of device migration potential. The pressure conditions specified in ISO 5840-1:2021, Tables 3 and 4, and other loading conditions, shall be considered as applicable. See ISO 5840-1:2021, Annex E for guidelines regarding suggested test conditions for the paediatric population.

7.2.6.3 Implant foreshortening (length to diameter)

The manufacturer shall determine the decrease in length of the implant between the catheter-loaded condition and the deployed diameters up to the maximum labelled diameter (see ASTM F2081 for guidance). The results shall be reported in terms of a percentage of the loaded length as shown below:

$$P_f = 100 \times (l_c / l_l)$$

where

P_f is the percentage of foreshortening;

l_c is the change in length;

l_l is the loaded length;

7.2.6.4 Crush resistance

The manufacturer shall determine the ability of the support structure to resist permanent deformation due to crushing loads acting at the intended implant site over a diameter range per the product specification. For non-circular devices, an account shall be taken of the specific use range of the device as it relates to the intended annulus geometry (e.g. anterior to posterior dimension or commissure to commissure as it relates to the mitral annulus). This is accomplished by the following evaluations:

— the crush resistance test with a radially applied load measures the ability of the support structure to resist permanent deformation when subjected to a circumferentially uniform radial load;

— the crush resistance test using parallel plates measures the ability of the support structure to resist permanent deformation along the entire length of the device when subjected to a load applied over the length of the device.

7.2.6.5 Recoil

The manufacturer shall determine the amount of elastic recoil in device diameter (percentage of device diameter reduction) after implant expansion. This shall be assessed against the recommended sizing given in the product specification. See ASTM F2079 for guidance.

7.2.6.6 Radial resistive force (RRF)

The manufacturer shall characterize the force exerted by the support structure as it resists radial compression from its maximum diameter to its minimum crimped diameter as shown in the device specification. See ASTM F3067 for guidance. Consideration shall be given to the effect of multiple crimping or retrieval steps as appropriate for the device. For non-symmetric devices, the perimeter change or other dimensions shall be considered.

7.2.6.7 Chronic outward force

The manufacturer shall characterize the force exerted by the support structure as it attempts to expand to its maximum unconstrained diameter after being radially compressed to its minimum crimped diameter per the device specification. See ASTM F3067 for guidance. Depending on the support structure design, the COF might be different in different regions of the support structure and shall be evaluated accordingly. Consideration shall be given to the effect of multiple crimping or retrieval steps as appropriate for the device. Non-symmetric devices shall consider perimeter change or other dimensions.

7.2.6.8 Delivery system design evaluation requirements

The manufacturer shall define and justify all applicable requirements based on the results of the risk assessment for the specific delivery system design and delivery approach (e.g. transfemoral, transapical). See Annex D for information on delivery system design evaluation requirements.

7.2.6.9 Visibility

The ability to visualize the implanted device and delivery system during delivery, deployment and during/after delivery system withdrawal, using the manufacturer's recommended imaging modality (e.g. fluoroscopy, MRI, CT, echocardiography) shall be evaluated. See Reference [18] for information relevant to TMVI. For ViV and ViR indications, the ability to visualize the implant and delivery system in the presence of an existing prosthesis shall be evaluated.

7.2.7 Device MRI compatibility

The requirements shall be as specified in ISO 5840-1:2021, 7.2.7.

7.2.8 Simulated use

The requirements shall be as specified in ISO 5840-1:2021, 7.2.8.

The ability to permit safe, consistent and accurate deployment of the transcatheter heart valve substitute within the intended implant site shall be evaluated using a model that simulates the intended use conditions. This assessment will include all elements of the transcatheter heart valve system and all associated procedural steps required to facilitate delivery and implantation of the implantable device (see Annex D).

The model shall consider anatomical variation with respect to delivery pathway and intended implant site as well as physiological and mechanical factors (e.g. temperature effects, pulsatile flow, frictional effects). In the case where device anchoring relies on specific interactions with the native anatomy (e.g. native leaflets, annulus), testing shall be included in the simulated use evaluation. Further, in the case of deployment of the transcatheter heart valve substitute within a pre-existing prosthetic device, the model shall consider the dimensions and conditions (e.g. calcification) of the existing device. The simulated use test shall evaluate inaccurate valve positioning and deployment and the resulting effects on valve performance and unintended anatomical interactions (e.g. coronary occlusion, anterior mitral impingement, LVOT obstruction, systolic anterior motion, chordae entanglement, valve embolization in ViV or ViR).

7.2.9 Human factors and usability assessment

The requirements shall be as specified in ISO 5840-1:2021, 7.2.9.

7.2.10 Implant thrombogenic and haemolytic potential assessment

The requirements shall be as specified in ISO 5840-1:2021, 7.2.10.

For transcatheter valves, the assessment shall include the immediate vicinity (e.g. neo-sinus, neo-LVOT, inflow and outflow) of the heart valve substitute, including within the valve, leaflet commissures, and cusps.

7.3 Preclinical *in vivo* evaluation

7.3.1 General

The general requirements of ISO 14630 shall be considered.

7.3.2 Overall requirements

A preclinical *in vivo* test programme shall be conducted for new or modified transcatheter valve systems in order to address the safety and performance of the heart valve substitute. For design modifications to a heart valve substitute system with established clinical history, omission or abbreviation of preclinical *in vivo* evaluation shall be appropriately justified.

The preclinical programme design shall be based on risk assessment and appropriate ISO guidance documents. This programme may involve the use of different species and implant durations to address the key issues identified in the risk assessment.

The preclinical *in vivo* evaluation shall:

a) evaluate the haemodynamic performance of the transcatheter heart valve substitute;

b) assess delivery, deployment, implantation procedure and imaging characteristics of the transcatheter heart valve system. All usability characteristics that are evaluated shall be completed consistent with the requirements of IEC 62366 (all parts). Consideration shall be given, but not limited, to the following items:

   1) usability, including delivery system handling characteristics (e.g. pushability, trackability);

   2) proper valve alignment relative to flow (e.g. note the presence of device angulation, bends, kinks);

   3) post-implantation changes in shape and structural components of the transcatheter heart valve;

   4) imaging characteristics;

   5) migration or embolization of the heart valve substitute;

   6) interaction with surrounding anatomy such as leaflets, annulus and subvalvular structures;

   7) ability to deploy, recapture, retrieve, reposition and/or remove the heart valve substitute, where applicable;

c) assess the *in vivo* response to the heart valve substitute. Consideration shall be given, but not limited, to the following items:

   1) healing characteristics (e.g. pannus formation, tissue overgrowth);

   2) effect of post-implantation changes in shape and structural components (e.g. the presence of device angulation, bends, kinks) on haemodynamic performance;

   3) haemolysis;

   4) thrombus formation;

   5) embolization of material from the implant site, delivery device or heart valve substitute;

   6) migration or embolization of the heart valve substitute;

   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 valve deterioration and/or non-structural valve dysfunction;

d) use the final design of the transcatheter heart valve system. Where applicable, the system shall be prepared, deployed, recaptured, retrieved, repositioned and/or removed and imaged using the same procedures as intended for clinical use. Consideration shall also be given to effects of maximum allowable conditioning steps (e.g. maximum sterilization cycles, maximum crimp time,

maximum crimp cycles, maximum time to maintain the implant in the crimped state, maximum retrieval and repositioning events if indicated in the device specification);

1) if needed, ancillary studies could be conducted to evaluate unique design and delivery aspects of the device;

2) the manufacturer shall justify any modifications to the device or system that may be required for implantation in the animal model and address the impact of the modifications on the interpretation of results;

e) investigate the transcatheter heart valve substitute system in positions for which it is intended (e.g. aortic, mitral, pulmonic); if species-specific anatomical features or the use of a non-diseased animal model confound the ability to evaluate the transcatheter heart valve substitute in positions for which it is intended, provide a justification for implantation in an alternative site or the use of alternative implantation procedures;

f) subject comparably sized control valve substitutes to identical anatomical and physiological conditions as the test valve; if a control valve is not used, the manufacturer shall provide a justification;

g) be performed by appropriately experienced and knowledgeable test laboratories under appropriate quality assurance standards (e.g. good laboratory practice);

h) address animal welfare in accordance with the principles provided in ISO 10993-2.

7.3.3 Methods

Guidance on the conduct of *in vivo* preclinical evaluation and a series of tests which can be used to address the relevant issues is provided in Annex F. The intent of these studies is to mimic as closely as possible the clinical use and haemodynamic performance of the transcatheter heart valve system (delivery, deployment, imaging and test heart valve substitute). It is recognized that adverse events (AE) arising after valve implantation can be attributed to the implanted valve, the procedure, and/or the environment into which it is implanted, including interactions among these. Therefore, serious adverse events (SAE) arising during or after valve implantation shall be carefully analysed and interpreted in order 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 and age). The test heart valve substitute shall be assessed in anatomical positions for which it is intended to be used clinically. Animals suffering from periprocedural complications not related to the heart valve system (e.g. endocarditis) may be excluded from the group of study animals, but they shall be reported.

The number of animals used for implantation of test and control valve substitutes and study endpoints shall be justified based on risk assessment.

For all studies, the specified duration of the observation period of the animals shall be justified according to the parameter(s) under investigation. New devices (e.g. new design or novel blood-contacting materials) require an extended duration of the observation period (not less than 140 d). A minimum duration less than 140 d may be suitable for evaluating minor modifications of an existing transcatheter heart valve system, such as investigations of healing. Any pre-clinical investigation with a designated endpoint of less than 140 d 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/device related pathology. The report shall include this information from all animals that have been entered into the study.

The study shall include at least the following:

a) *in vivo* evaluation of the final device and system design;

b) any detectable pathological consequences, including but not limited to: migration or embolization; paravalvular leakage; valve alignment relative to flow noting the presence of angulations, bends or kinks; post-implantation changes in shape of structural components; thrombo-embolic phenomena; pannus formation; and tissue disruption and/or inflammatory responses involving the transcatheter heart valve substitute and/or in the major organs;

c) any detectable structural alterations (macro- or microscopic or radiographic) in the transcatheter heart valve substitute and macroscopic examination of the delivery system (e.g. damage, support structure fracture, 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, deployment, recapturability, retrieval, repositionability and/or removal (if applicable);

f) haemodynamic performance over a range of cardiac outputs (e.g. 2,5 l/min to 6,0 l/min) in the same animal;

g) adverse events (e.g. myocardial infarction, significant cardiac arrhythmias, infection, embolization, major paravalvular leakage);

h) any other system or procedure-related complication or events.

7.3.4 Test report

The laboratory performing the preclinical *in vivo* study shall produce the test report based on the original study protocol, including:

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

b) detailed description of the animal model used, and the rationale and justification for its use; the pre-procedural assessment of each animal shall include documentation of health status as well as gender, weight and age of the animal;

c) description of the imaging technique(s), the implantation procedure, including delivery, deployment and sizing technique, valve position and any procedural difficulties;

d) description of the pre-procedural and post-procedural course of each animal including clinical observations, medication(s) and interventions used to treat adverse events; describe and justify any anticoagulation or antiplatelet drug and regimen used as well as therapeutic level monitoring methods, if applicable;

e) any deviation from the protocol or amendments to the protocol and their significance;

f) names of the investigators and their institutions along with information about the implanting personnel and the laboratory's experience with heart valve substitute implantation and animal care;

g) interpretation of data, including a comparison of the results between test and control animals, and a recommendation relative to the expected clinical safety and performance of the transcatheter heart valve 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 substitute;

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 assumed to be caused by the heart valve substitute;

j) a summary of all data generated from all animals during the course of the investigation. In particular, serious adverse events generated by evaluations described in Annex F, as well as deviations from the protocol and their significance, shall be addressed.

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 transcatheter heart valve systems and expanded indications for use of existing systems (e.g. lower risk populations, ViV, ViR). For modifications of an existing transcatheter heart valve system, if a determination is made, based on the risk analysis, that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided. For minor design modifications to clinically well-documented heart valve substitutes, the manufacturer shall justify omission or abbreviation of clinical investigations.

Clinical studies are recommended for design changes of a marketed device that may 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). The clinical study design, sample size, and endpoints shall be justified based upon the risk analysis for design changes/device modifications under evaluation.

Clinical investigations shall be designed to evaluate the transcatheter heart valve system for its intended use. The studies shall include an assessment of adverse events related to risks arising from the use of the transcatheter heart valve system and from the procedure. The clinical investigation shall include pre-procedure, peri-procedure, and follow-up data from a specified number of subjects, each with a follow-up appropriate for the device and its intended use. The clinical investigation programme shall be designed to provide substantial evidence of acceptable safety and effectiveness to support the intended labelling for 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 device performance. 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 transcatheter heart valve system and patient selection prior to initiation of a larger clinical investigation following further pre-clinical testing.

A pivotal clinical investigation shall be designed to ensure:

a) the presence of a well-defined, clinically relevant question;

b) an acceptable level of risk-benefit for the patient considering the available alternatives and standard of care;

c) an appropriate study design to answer the clinical question, including a well-defined patient population, study endpoints and duration.

A randomised study design for a pivotal trial should be considered for the following reasons:

a) ethical considerations may require a head-to-head comparison with scientifically justified alternative treatments or standard of care;

b) randomised trials provide the highest quality scientific evidence and minimize bias;

c) randomised trial results may promote adoption of effective therapies.

For clinical investigations to serve as a basis for market approval, there should be sufficient data to support safety and effectiveness. These studies should include a statistical methodology, specific inclusion/exclusion criteria, use of accepted endpoint definitions, a rigorous method 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.

ViV/ViR clinical investigation may be a separate evaluation of the specific indication or included as an arm of a larger clinical investigation. For clinical investigations to evaluate ViV/ViR indications, 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

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 or the risk and anticipated benefits of alternative procedures (the requirements shall be as specified in ISO 14971).

With transcatheter heart valve systems, haemodynamic performance and those adverse events which are directly related to the device or procedure should be measured to assess risk (e.g. coronary obstruction, LVOT obstruction). Haemodynamic and clinical performance including adverse events may also depend on factors other than the device itself, including:

a) patient comorbidities;

b) the underlying pathological process and whether it continues to progress;

c) whether the degree of functional improvement achieved is sufficient to prevent progressive deterioration in cardiac function;

d) technical factors involved in delivery, choice of vascular access and implantation;

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

f) the potential for adverse haemodynamic effect.

See Annex G for more information about adverse events.

Imaging assessment is an essential aspect of the clinical investigation for patient selection, device placement, avoidance of procedural complications and patient follow-up. To ensure optimal anatomical evaluation, device position, and functional assessment, multiple imaging modalities (e.g. TEE, TTE, CT, MRI, fluoroscopy, positron emission tomography (PET)) may enhance assessment and shall be used where applicable (see also Annex H). The latest imaging guidelines from professional societies should be followed in performing these imaging procedures to ensure the quality of images. Clinical site training and certification shall be conducted before enrolment in collaboration with the independent core laboratory (see Reference [23]). 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 clearly define the objectives of the study and specify safety and effectiveness endpoints (see Annex G and ISO 5840-1:2021, Annex L). The CIP shall specify anticipated study-related adverse events, including device and/or procedure-related adverse events, in accordance with Annex G and published definitions. The definitions of the outcome measures should be consistent with those described in this document to allow comparability of heart valve systems. The study design shall include a pre-specified statistical analysis plan and success criteria (e.g. new devices should be non-inferior to standard of care).

Studies should employ measures to minimise 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. However, depending on local legal requirements, additional follow-up may be obtained.

The manufacturer is responsible for ensuring collection of appropriate information. The study design shall be consistent with the aims of the CIP. For a given study, the CIP and data collection forms should be standardized across institutions and investigators.

Study monitoring shall be conducted in accordance with ISO 14155. To ensure patient safety, a safety monitoring plan shall be established. Study oversight shall be provided by an independent data safety monitoring board (DSMB) for evaluation of patient safety and CIP adherence. The monitoring board is empowered to make recommendations for or against study continuation. An independent clinical events adjudication committee shall be used to classify events against pre-established criteria. Core laboratories are recommended for outcomes that might be prone to inter-laboratory variability for pilot phase (at multiple sites) studies and are required for pivotal studies.

Explant analysis is a vital part of device evaluation. Devices explanted or obtained at post-mortem examination should be assessed by an independent cardiovascular pathologist. The results of analyses should be reported in accordance with the CIP including operative or post-mortem examination 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 post-mortem examination photographs) and instructions for the return of the explanted device to the manufacturer, where appropriate. Whenever feasible, the explanted device shall be subjected to appropriate functional, imaging and histopathological investigations. In the event of subject death, valuable information about implanted devices can be obtained by post-mortem examination, which should be encouraged whenever possible.

The following considerations apply for pilot phase studies:

a) pilot phase studies are exploratory in nature and may not require pre-specified statistical hypotheses. Robust interpretation of the results and their generalizability is usually limited due to the small number of subjects and participating clinical investigators;

b) 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) 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 (CEC) should be used for adjudication of adverse events;

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

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

7.4.3 Study endpoints

The choice and timing of primary and secondary study endpoints shall be driven by the study objectives, the disease, the patient population, the technology, the post-operative medical treatment (e.g. heart failure treatment, antithrombotic medication) and anticipated risks. Endpoints 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 endpoints should be considered relative

to the technology. Further suggestions for clinical investigation endpoint selection and timing for transcatheter heart valve systems are provided in ISO 5840-1:2021, Annex L.

7.4.4 Ethical considerations

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

The choice of patients to receive the first implants of a novel technology places responsibility on both manufacturers and investigators and raises important ethical issues. Choice of objective and skilled investigators who will implant the new device is equally important. Relevant guidance on conflict of interest has been provided by regulatory agencies or other organizations (see Reference [20]). Manufacturers shall not offer financial incentives to the institution or investigators to implant the device. Compensation of patients for the costs for participating in the clinical investigation shall be limited to an appropriate amount in line with ISO 14155, shall not be so large as to encourage patients to participate.

NOTE National regulations apply.

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

7.4.5 Pivotal studies: 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 [24] and [26]). Clinical investigations shall be designed to include enough subjects, investigators, and institutions to be representative of the intended patient and user populations. The design should include consideration of, and justification for, such aspects as disease aetiology, disease severity, gender, age (e.g. adult, paediatric) and other special patient populations as appropriate. The sites should be selected 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 the 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 maximum number of 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 selection of sites and clinical investigators should include:

— Sites:

a) suitable distribution of sites;

b) access to the defined patient population;

c) presence of a local or central institutional review board (IRB)/ethics committee (EC);

d) qualified centres, following the guidelines on operator and institutional requirements published jointly by the professional societies (see Reference [26]);

e) involvement of a multi-disciplinary heart team in patient selection including at least one non-conflicted physician;

f) expert imaging with accredited operators and facilities (see also Annex H);

g) appropriate study coordinator and other administrative staff associated with data collection or coordination of the study;

h) adequate resources (e.g. facilities and equipment, security and storage, working space for monitor and additional equipment);

i) accordance with good clinical practice (GCP), including but not limited to: regulatory agency and IRB/EC approval prior to study initiation; proper consenting of all research subjects; CIP adherence, with any deviation properly approved or documented; proper adverse event reporting; and adequate device accountability;

j) experience with clinical investigations;

k) acceptable results of previous regulatory inspections.

— Clinical investigators:

a) qualifications by education, training (by manufacturer or medical experts), relevant experience;

NOTE Regulatory requirements can apply.

b) motivation to continue patient recruitment and to undertake long term accurate follow-up;

c) prior clinical research experience;

d) avoidance of competing studies (e.g. to avoid selection, channelling biases);

e) minimising potential conflict of interest; if there are substantial conflicts of interest with the manufacturer, such conflicts shall 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 [10] and [20]).

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 randomised controlled trial, assessing superiority or non-inferiority as appropriate, may be considered to minimise bias. Depending on the scope and objectives of the clinical investigation, other designs may be appropriate.

The decision to use a medical device in the context of a particular clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure in comparison with the risk and anticipated benefits of alternative procedures (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, randomisation against an appropriate active comparator with established clinical history 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 safety and performance or effectiveness endpoints of the transcatheter heart valve system in the intended populations. Standard statistical methods shall be used to calculate the minimum sample size with prior specification of an appropriate Type 1 error rate

and power. Sample size considerations shall also take into account the standard of care and available safety and performance or effectiveness data (including post-market or published data) on relevant therapies with similar intended use.

For a new transcatheter heart valve system, in a population with acceptable surgical risk, the sample size shall include a minimum number of 150 patients 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, valve thrombosis, haemorrhage, and 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. For clinical investigation with low anticipated event rates, the associated patient year follow up may be derived from Table 3 (e.g. at least 972 follow-up years for a 1 %/year event rate). This aligns with sample size requirements for surgical heart valve replacement devices (see ISO 5840-2:2021, 7.4.6.2).

If the population to be studied is an orphan disease population or not of acceptable risk to allow appropriate treatment or therapy (e.g. medical, surgical, interventional) to be undertaken, a smaller sample size may be justified based on a robust statistical analysis which takes into consideration the anticipated risk benefit profile. The approved indication for use shall be consistent with evidence gained from the patients studied. Departures from the recommended 400-patient year sample size shall be adequately justified. Table 3 below provides a range of sample sizes that exclude an adverse event rate that is double the expected rate.

Table 3 — 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 (H0) (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

NOTE The recommendation to collect 400-patient years of data is based upon the following considerations: using a null hypothesis that the actual adverse event rate is twice the event rate currently accepted for similar devices (see Reference [14]), with probabilities of one-sided type one error of 5 % and probability of type 2 error 20 % (power = 80 %), the sample size (in patient-years) is determined to be 9,72/CR, where CR is the complication rate currently considered acceptable for similar devices. For example, to detect a CR of 2,4 %/year or higher, this would require 9,72/0,024 = 400 patient-years (see References [15] and [12]).

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 may 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.

In addition to the requirements established above, the CIP shall specify total duration of the study, including long-term patient follow-up which may continue in the post-market setting (see also 7.4.9.6). The study duration shall be established based on the specific purposes of the study as identified by the risk assessment, the intended application, the outcomes measured, and, if relevant, the type of device

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

7.4.7 Patient selection criteria

The inclusion and exclusion criteria for patient selection shall be clearly defined. The intended patient population shall be specified and any salient differences between the intended population and those studied shall be justified. The study should only include patients 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);

b) disease aetiology (e.g. stenosis, primary or secondary regurgitation);

c) severity of valve disease;

d) symptomatic versus asymptomatic patients;

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

f) co-morbidities (e.g. MI, other valve disease, coronary or peripheral artery disease, atrial septal defect, patent foramen ovale, previous infective endocarditis, rheumatic heart disease, degenerative neurological disorders, frailty, previous cardiac interventions, prior stroke or systemic embolism, chronic kidney disease, haematologic disorders, chronic lung disease);

g) ventricular function and chamber size (e.g. ejection fraction, systolic/diastolic dimension or volumes);

h) haemodynamic stability (e.g. mechanical circulatory assist devices, inotropic support);

i) surgical status (e.g. elective, urgent, emergency, salvage);

j) tolerance for procedural/post-procedural anticoagulation or antiplatelet regimens;

k) life expectancy;

l) device/procedure specific anatomical considerations (e.g. valve size, calcification, congenital abnormalities, access site conditions, device placement location, ability to tolerate TEE);

m) potential patient-prosthesis mismatch;

n) access to sufficient follow up treatment (all types of physical and medicinal therapy).

7.4.8 Valve thrombosis prevention

The approach to be employed to prevent valve thrombosis and thromboembolic complications shall be documented in the CIP and recorded on the CRF. In addition to details of antithrombotic and/or antiplatelet drug therapy (including INR range, where applicable), the approach shall include details and results of any investigations performed to detect subclinical valve thrombosis as a basis for choosing an appropriate drug therapy.

7.4.9 Clinical data requirements

7.4.9.1 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 laboratory adjudicated data.

7.4.9.2 Baseline

The following data shall be collected:

a) patient demographics (e.g. age, gender);

b) baseline information (e.g. weight, height, blood pressure);

c) co-morbidities (e.g. liver, kidney and lung disease, substance abuse, smoking history, diabetes, hypertension, hypercholesterolemia);

d) cardiovascular diagnosis (e.g. valvular lesion and aetiology) and co-existing cardiovascular diseases (e.g. heart failure, cardiomyopathy, aneurysm, cerebral vascular disease, peripheral vascular disease, coronary artery disease, history of endocarditis, history of thromboembolism, previous myocardial infarction), and cardiac rhythm;

e) New York Heart Association (NYHA) functional class and relevant Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score or logistic European System for Cardiac Operative Risk Evaluation (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;

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 (type, size and position), root reconstruction, peripheral vascular interventions];

g) echocardiographic and other relevant imaging data to provide cardiac haemodynamic, geometric and functional information (e.g. ventricular function), and to characterize the diseased valve or failed prosthesis/repair and to assess implant site and annulus size (see Annex H and ISO 5840-1:2021, Annex G);

h) relevant imaging data for assessment of access and delivery approach;

i) blood test to assess hepatic, cardiac and renal status, and haematologic/coagulation profile.

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

7.4.9.3 Peri-procedure data

The following data shall be collected:

a) name of operator(s);

b) utilisation time (e.g. procedure room entry/exit time, access site entry/exit time, length of hospital stay);

c) date/time of procedure;

d) type of procedure suite (e.g. operating room, hybrid room, cardiac catheterization laboratory);

e) methods of anaesthesia (e.g. general, local, conscious sedation);

f) medications including start/stop dates, dosage, changes, change justification (e.g. antithrombotic regimen, inotropes, antibiotic prophylaxis);

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

h) list of monitoring devices used (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. ACT, 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);

k) any changes from original diagnosis;

l) transcatheter heart valve system (e.g. type, models, sizes, and serial numbers);

m) any concomitant interventions or procedures (e.g. percutaneous coronary intervention (PCI));

n) elements of procedure, including any adjunctive procedures performed (e.g. pre-dilatation, post-dilatation, contrast volume, 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) size, type, implant date, presence of patient prosthesis mismatch (PPM), and failure mode of previously implanted prosthesis for a valve in valve/ring procedure;

s) assessment of handling, visualization, deployment, orientation, implant location and insertion/withdrawal of delivery system, where appropriate;

t) number of re-sheathings and recapturing for proper positioning;

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

v) evaluation of transcatheter heart valve function and valve geometry by echocardiography and/or other relevant imaging and haemodynamic modalities, as defined in the CIP. At a minimum, pressure gradient and degree of regurgitation should be documented;

w) 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.

7.4.9.4 Follow-up data

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

NOTE Additional follow-up intervals might be appropriate to document early or long-term structural valve deterioration or non-structural dysfunction.

The following data shall be collected:

a) date, method (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) New York Heart Association functional class and health-related quality of life indicator(s);

d) functional assessment (e.g. 6 min walk test, peak VO_2);

e) device assessment (e.g. structural integrity, thrombus deposition); see Annex H; the selection criteria for all patients shall be documented in the CIP;

   1) for pilot and pivotal studies of transcatheter aortic valves, an enhanced CT imaging study of the prosthesis shall be performed for all patients or a well-defined and scientifically justified subset within the first 3 months;

   2) for pilot and pivotal studies of transcatheter mitral valves, a TEE study shall be performed on all patients within the first 3 months;

f) haemodynamic evaluation by Doppler echocardiography, or other relevant methodology (the methodology chosen should be consistent for consecutive studies, see ISO 5840-1:2021, Annex G);

g) heart rate, rhythm and conduction abnormalities;

h) tests for haemolysis (e.g. plasma-free haemoglobin); other blood tests may be indicated; haemolytic anaemia shall be reported as non-structural valve dysfunction;

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

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

k) adverse events as specified in Annex G;

l) concomitant therapies, that can include cardiac assist and need for pacing;

m) date and reason for reintervention (e.g. surgical, percutaneous, ViV);

n) date and cause of death;

o) explant analysis and post-mortem examination report, if performed; explant analysis shall include histological assessment to document the extent of thrombus and/or fibrous tissue, if present on the leaflets; see Reference [25]; the post-mortem examination 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.

7.4.9.5 Clinical investigation analysis and reporting

The clinical investigation report shall be in accordance with ISO 14155. The clinical investigation report shall include information on all subjects for whom implantation was planned (i.e. the "intent-to-treat" population). For randomised studies, the groups shall include all randomised subjects, even those who did not receive the implant. Additional analyses shall be performed on the subjects who actually received the implant (see also Annex H and ISO 5840-1:2021, Annex L). Justification shall be provided for those who were randomized to but did not receive an implant.

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

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

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

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 post-mortem examination data and explant data if available; reliance on national healthcare databases to simply record that death has occurred is insufficient; a high percentage of unknown cause of death may raise suspicion of device-related deaths.

7.4.9.6 Post-market clinical follow-up

Prolonged post-market follow-up is essential in order to capture long-term data on less common or unanticipated adverse events, on adverse events which are time-related (e.g. structural deterioration, adverse effects on 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 would 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 justified and 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 a minimum of 10 years post-implant shall be conducted on the pivotal phase cohort with endpoints designed based upon risk assessment and device claims. The 10-year post-implant study should collect safety and performance and effectiveness data (e.g. death, cause of death, stroke, thromboembolism, quality of life, valve re-intervention). In certain situations, 10-year follow-up might not be feasible (e.g. high-risk patients, elderly) and the follow-up duration shall be justified.

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

Follow-up should be as complete as possible avoiding retrospective self-reporting and reports should include follow-up years to allow calculation of adverse event rates, in order to generate 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. Registry data shall be regularly reviewed, and alert mechanisms should also be in place to trigger additional safety reviews based on pre-specified criteria.

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

The following 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 effectiveness of the device;

b) a statement of percent follow-up completeness shall be provided;

c) 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;

d) 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;

e) information on cause of death is particularly important, as emphasised in 7.4.9.5.

Annex A
(informative)

Description of the transcatheter heart valve system

A.1 General

This annex contains a listing of terms that may be used in describing transcatheter heart valve system components in device documentation (e.g. labelling, IFU).

A.2 Description of the transcatheter heart valve substitute

The description of the transcatheter heart valve substitute should include, at a minimum, the information listed below. The description should be supported by pictures or illustrations where appropriate.

— Components (e.g. leaflets, support structure, connections to leaflets, connections to annulus);

— Occluder/leaflet materials (e.g. pericardial, venous valve);

— Structural materials (e.g. stainless steel, nitinol);

— Component joining materials/methods (e.g. suture materials);

— Deployment mode (e.g. self-expanding, balloon expanding, mechanically expanding,);

— Implant position (e.g. aortic, mitral, tricuspid, pulmonic, conduit);

— Deployed valve diameter or diameter range;

— Connection or interaction of the device with the intended implant site;

— Retrievability;

— Ability to be placed in a specific orientation.

A.3 Description of delivery system

The description of the delivery system should include, at a minimum, the information listed below. The description should be supported by pictures or illustrations where appropriate.

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

— Delivery tools/catheters;

— Guidewire;

— Introduction sheath;

— Balloon;

— Crimping/loading tool;

— Access port;

— Accessories.

A.4 Chemical treatments, surface modifications or coatings

The description should include any chemical treatments, surface modifications or coatings used, including primary fixation of tissue and any anti-calcification, anti-infection or anti-thrombotic treatments.

A.5 Component description

Each of the components of the transcatheter heart valve substitute should be listed and the materials of construction, including colorants, should be documented. The components list should include packaging storage solution (e.g. for tissue materials). An assembly sketch should be documented that includes all components, including joining materials, such as sutures.

A.6 Implant procedure

A detailed description of the implant procedure, including procedures for sizing the valve, should be provided.

Annex B
(informative)

Transcatheter heart valve substitute hazard analysis example

B.1 Hazards, foreseeable sequence of events, hazardous situations, and associated harms

It is the responsibility of the manufacturer to establish a comprehensive list of hazards and associated harms for the transcatheter heart valve system. The manufacturer should consider both the indicated use and anticipated use of their device (e.g. deployment into a pre-existing prosthetic device). Table B.1 is an example that is intended to demonstrate the linkage among potential hazards, foreseeable sequence of events, hazardous situations, and harms for transcatheter heart valve systems based on the framework provided in ISO 14971. The example shown is not intended to be all-inclusive. An example hazard analysis for TMVI devices can be found in Reference [18].

Table B.1 — Example transcatheter heart valve substitute hazards, foreseeable sequence of events, hazardous situations, and associated harms

Hazard	Foreseeable sequence of events	Hazardous situation	Harm
Valve frame radial force	Valve with insufficient radial force migrates to an unintended implant position	Final location of valve results in contact with conduction system	Arrhythmia
	Inappropriately oversized valve implanted	High force exerted by valve creates contact with conduction system	
	Inadequate conformance of the frame to the annulus	a) Excessive paravalvular leak b) Excessive transvalvular gradient	a) Heart failure b) Haemolysis
Implantation error	Device implanted in unintended position	Final location of valve results in contact with conduction system	Arrhythmia
		Final location of device creates neo-sinus that cannot be effectively washed out resulting in thrombus formation	Thromboembolic events
		Inadequate sealing around the valve leading to excessive paravalvular leak and gradient	a) Heart failure b) Haemolysis
	Excessive oversizing leading to selection of a larger valve than necessary / under-expansion	Redundant leaflet material leading to impaired leaflet mobility and decreased device durability resulting in structural valve deterioration	a) Heart failure b) Thromboembolic events
	Undersizing leading to selection of a smaller valve than necessary / under-expansion	Radial force exerted by valve on anatomy is insufficient leading to excessive paravalvular leak and gradient	a) Heart failure b) Haemolysis

Table B.1 *(continued)*

Hazard	Foreseeable sequence of events	Hazardous situation	Harm
	Over-expansion	Leaflets overstretched leading to inadequate coaptation and excessive transvalvular regurgitation	Heart failure
		Frame subject's annulus to excessive radial force	a) Annular rupture b) Annulus tissue damage
Delivery system profile	Delivery system profile too large for patient vessel anatomy	Delivery system overextends vessel	a) Vessel dissection b) Vessel perforation c) Vessel luminal damage d) Bleeding complications
Delivery system stiffness	Delivery system too stiff to track through tortuous anatomy	Delivery system perforates vessel in tortuous area	a) Vessel dissection b) Vessel luminal damage c) Bleeding complications
Protruding frame edges	Exposed valve frame edges contact vessel wall	Frame edges damage vessel during tracking	a) Vessel perforation b) Vessel luminal damage c) Bleeding complications
	Frame fracture after implant, resulting in a sharp edge	The sharp frame edge comes to contact with the annulus	a) Annular rupture b) Annulus tissue damage c) Bleeding complications

Annex C
(informative)

Guidelines for verification of hydrodynamic performance — Pulsatile flow testing

C.1 General

This annex provides guidance on test equipment, test equipment validation, formulation of test protocols, test methods and test reports for the hydrodynamic performance characterization of transcatheter heart valves. Equipment and test procedures should be appropriate for the valve's intended use, e.g. adult/paediatric, left/right-side, native valve/pre-existing prosthesis.

C.2 Pulsatile-flow testing

C.2.1 General

Pulsatile flow testing is intended to characterize the performance of the transcatheter heart valve substitute in physiological and pathological hydrodynamic conditions. Pulsatile testing broadly encompasses two separate objectives — comparison to minimum performance criteria provided in Tables 1 and 2 and comparative characterization across a range of cardiac conditions. For definitions relevant to pulsatile flow testing, refer to the definitions provided in ISO 5840-1:2021.

C.2.2 Measuring equipment accuracy

C.2.2.1 The pressure measurement system should have an upper frequency limit (−3 dB cut-off) of at least 30 Hz and a differential measurement accuracy of at least ±0,26 kPa (±2 mmHg). The flow meter should have an upper frequency limit (−3 dB cut-off) of at least 30 Hz.

C.2.2.2 Regurgitant volume measurements should have a measurement accuracy of at least ±2 ml.

C.2.2.3 All other measurement equipment should have a measurement accuracy of at least ±5 % of the maximum intended test measurement.

C.2.3 Test apparatus requirements

C.2.3.1 The pulsatile-flow testing should be conducted in a pulse duplicator which produces pressure and flow waveforms that approximate physiological conditions over the required physiological range appropriate for the intended device application in accordance with ISO 5840-1:2021, Tables 3 and 4. See ISO 5840-1:2021, Annex E in for guidelines regarding suggested test conditions for the paediatric population.

Characteristics of reasonable aortic and mitral physiological waveforms can be found in Reference [27].

C.2.3.2 It is recommended that manufacturers complete pulse duplicator system performance characterization prior to the start of design verification testing.

A round robin study was conducted across multiple industry and academic test laboratories using St. Jude Masters Series mechanical valves. The results from this study are summarized in Table C.1 and may be used as a reference for performance characterization of a pulse duplicator.

It is recommended that manufacturers utilize mechanical valve types used for the round robin study (see Reference [27] for additional details and results summarized in Table C.1) to characterize the pulse duplicator system performance.

Table C.1 — Performance characterization of pulse duplicator testing using mechanical valves

Valve size mm	Position	Simulated cardiac output l/min	Beat rate beats/min	EOA cm^2 (mean ± sd)	Reg. fraction % (mean ± sd)
19	Aortic	5,0	70	1,3 ± 0,1	6,1 ± 1,3
25	Aortic	5,0	70	2,4 ± 0,2	8,9 ± 0,9
25	Mitral	5,0	70	2,3 ± 0,2	6,1 ± 2,0

NOTE 1 Results when using physiological saline with specific gravity of 1,005 and viscosity of 1,0 cP. All testing conducted at a mean arterial pressure of 100 mmHg.

NOTE 2 Fixture considerations can influence measured hydrodynamic performance. The manufacturer should ensure that the noise factors associated with fixturing are minimized.

NOTE 3 The following St. Jude Medical Masters Series mechanical valve model numbers represent different sewing ring configurations; however, the pyrolytic carbon valve assembly is the same for all model numbers for a given size and would provide similar hydrodynamic performance.

19 mm Aortic: 19AJ-501; 19AECJ-502; 19ATJ-503

25 mm Aortic: 25AJ-501; 25AECJ-502; 25ATJ-503

25 mm Mitral: 25MJ-501; 25MECJ-502; 25MTJ-503; 25METJ-504

C.2.3.3 The pulse duplicator should permit measurement of time-dependent pressures and volumetric flow rates.

C.2.3.4 The repeatability of the test system should be evaluated and documented.

C.2.3.5 Relevant dimensions of the intended implant site should be simulated.

C.2.3.6 The conduit geometry and mechanical properties should be representative of the intended implant site. For ViV and ViR indications, the heart valve substitute should be deployed into simulated operating configurations representative of the intended pre-existing prosthetic device.

C.2.3.7 The chamber should allow the observer to view and photograph at least the outflow aspect of the heart valve substitute at all stages of the cycle.

C.2.4 Test fixture parameters — Minimum performance testing (for transcatheter aortic valves only)

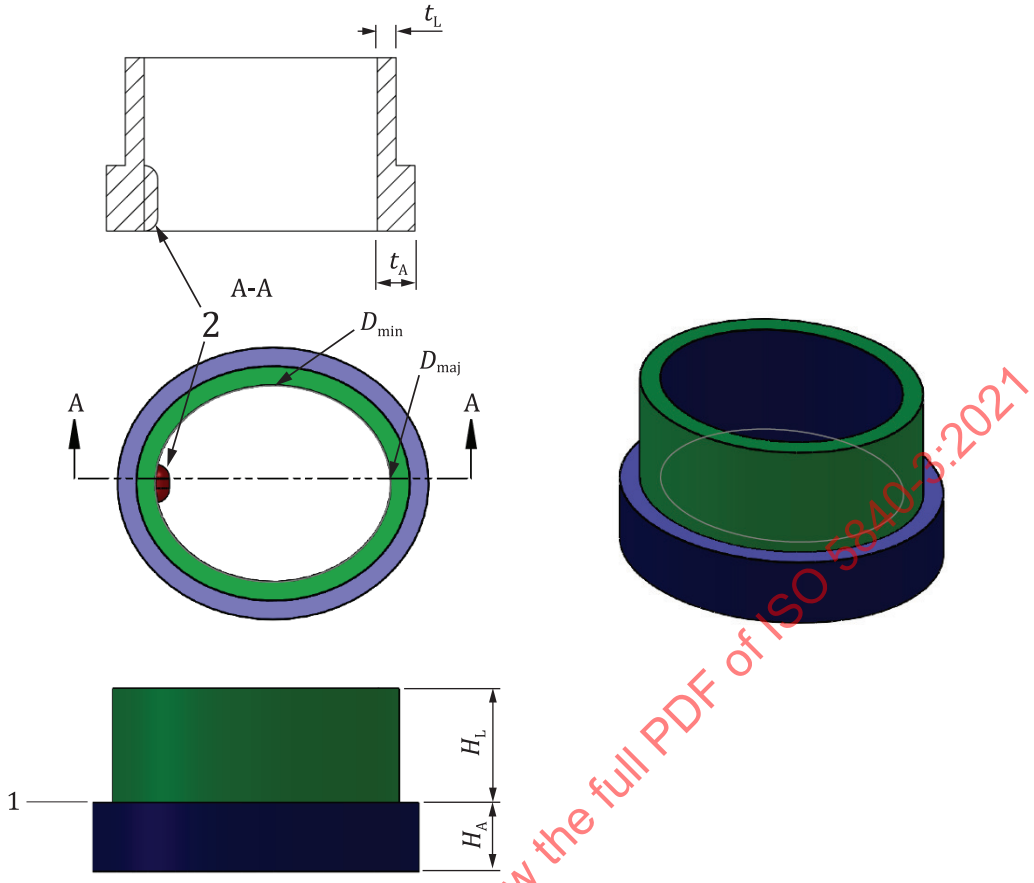
C.2.4.1 Table C.2 provides recommended aortic fixture parameters for evaluating the hydrodynamic performance of transcatheter aortic valves. The fixtures described in Table C.2 are intended to be simplified representations of typical implantation scenarios for trileaflet calcific stenosis for comparison to minimum performance requirements. See Figure C.1 for a schematic of a representative hydrodynamic test fixture. For other indications, such as bicuspid aortic valve disease, the manufacturer should define and justify the fixture parameters used.

C.2.4.2 This test fixture is not expected to be used for periodic hydrodynamic performance testing conducted during AWT.

C.2.4.3 The fixture attributes and recommended parameter ranges contained in Table C.2 were established based on review of published literature, review of clinical results for currently marketed TAVI devices, and *in vitro* testing conducted by manufacturers of currently marketed devices representing balloon-expandable, self-expanding and mechanically-expanding devices. The manufacturer should justify appropriately any parameters selected that differ from those in Table C.2 and clearly define parameters that are not specified in the table but are needed to meet manufacturer specific requirements. Testing of a commercially available reference valve of a similar design and construction may provide useful data during fixture development.

Table C.2 — Aortic fixture parameters

Attribute	Fixture parameters
Valve sizes	All available valve sizes
Annulus diameter, *D*	Smallest and largest diameter as recommended per product specification for each size.
Annulus ellipse ratio, R_e (Major diameter/ minor diameter)	1.0 (circular), 1.2 (ellipse). The elliptical configuration should have the same circumference as the circular fixture (see Figure C.1).
Annulus mechanical characteristics	Minimum thickness 4mm, minimum hardness Shore 10A, intended to simulate mechanical properties of implant site.
Annulus section height	Target range of 5-7 mm [the annular plane is defined as the aortic end of the annulus section (same as the base of the sinus)]. See Figure C.1.
Annular calcification (for devices intended to treat aortic stenosis only)	One “calcium nodule” with minimum 1,5 mm radial protrusion into the chamber, and minimum 4 mm circumferential extent. The nodule height should match the annulus section height. The nodule may be rounded to avoid sharp corners (maximum radius 1,5 mm). The calcium nodule should be made of a rigid material (see Figure C.2 for sketch of calcification nodule).
Leaflet height	0,5**D* (*D* is the annulus diameter) from the annular plane. 1mm - 2 mm thickness to simulate native leaflet (minimum 10A durometer). The shape of the leaflet should represent observations from clinical imaging (e.g. cylindrical leaflet region, tapered leaflet region).
Configurations	Testing should be conducted in all the configurations listed below, unless a worst-case condition is identified and justified: — circular with nodule; — 1.2 ellipse with nodule along major diameter; — 1.2 ellipse with nodule along minor diameter. NOTE For pure aortic insufficiency indications, testing can be conducted in a circular configuration without a nodule.
TAVI implant considerations	— Deployment depth at nominal condition within the manufacturer's recommended range. Deployment depth is measured from the annular plane. — Circumferential orientation of the device within the fixture to produce the highest amount of leakage.

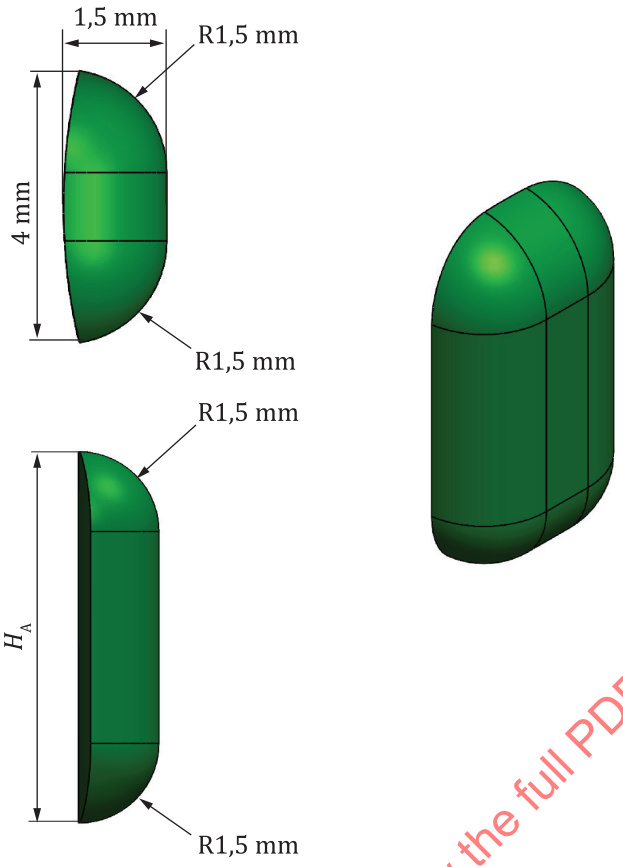


Key

1	annular plane
2	nodule
t_L	leaflet thickness
t_A	annulus thickness
D_{min}	minor diameter
D_{maj}	major diameter
H_L	leaflet height
H_A	annulus height

Figure C.1 — Representative schematic of TAVI hydrodynamic test fixture

NOTE This fixture depicts cylindrical shape of the native valve leaflet region.



Key

H_A annulus height

Figure C.2 — Schematic of simulated calcification nodule for TAVI hydrodynamic test fixture

C.2.4.4 In addition to testing in nominal fixtures, characterization should be conducted in challenge conditions that represent worst case implantation scenarios under nominal pulsatile flow conditions. No minimum performance criteria are provided for testing in challenge conditions; however, the manufacturer should justify the acceptability of these results relative to anticipated clinical scenarios. Examples of potential parameters for challenge conditions are listed below:

a) annulus ellipse ratio: based on expected worst case clinical deployment of device;

b) annulus section: non-compliant annulus section (severe annular calcification);

c) calcification: 2,5 mm radial protrusion of calcification with 0,2 mm edge radius;

d) TAVI implant considerations: worst-case deployment depth and worst-case circumferential orientation;

e) patient specific anatomical models.

C.2.4.5 Additional testing should be conducted for indications other than native trileaflet calcific aortic stenosis (e.g. bicuspid morphology, ViR, ViV).

C.2.5 Test fixture parameters — Minimum performance testing (for transcatheter mitral valves only)

C.2.5.1 Table C.3 provides recommended test fixture parameters for evaluating the hydrodynamic performance of transcatheter mitral valves. The fixtures described in Table C.3 are intended to represent

typical implantation scenarios, for comparison to minimum performance requirements. The fixture attributes contained in Table C.3 were selected based upon potential impact to hydrodynamic performance and were established based on review of published literature. At the time of the release of this document, sufficient clinical data were not available to specify parameter ranges for the attributes listed in Table C.3. Parameters should be defined and justified based on manufacturer specific requirements. Attributes not listed in the table may be considered and should be justified by the manufacturer.

Table C.3 — Mitral fixture parameters

Attribute	Fixture parameters
Valve sizes	All available valve sizes.
Annulus diameter, *D*	Smallest and largest resultant diameter as recommended per product IFU for each size.
Annulus ratio — Commissural-commissural (C-C) — Septal-lateral (S-L)	Justified by the manufacturer.
Annulus compliance	Annular compliance to target that of intended implant site or as justified by the manufacturer.
Annulus section height	Justified by the manufacturer.
Annular calcification (for devices intended to treat mitral regurgitation)	Fixture parameters shall be determined based on an analysis of the intended treatment population.
Leaflet length	Justified by the manufacturer.
Configurations	— Testing should be conducted in all the configurations listed below, unless a worst-case condition is identified and justified: — low end of use range; — high end of use range; — patient treatment population considerations (i.e. MAC, aortic devices).
TMVI implant considerations	— Deployment depth at nominal condition within manufacturer recommended range. Deployment depth is calculated from the annular plane. — Circumferential orientation to be assessed for worst case (e.g. C-C, S-L).

C.2.5.2 In addition to testing in nominal fixtures, characterization should be conducted in challenge conditions that represent worst-case implantation scenarios. No minimum performance criteria are provided for testing in challenge conditions; however, the manufacturer should justify the acceptability of the results relative to anticipated clinical scenarios.

C.2.6 Test parameters — Multi-range hydrodynamic characterization testing (all transcatheter valves)

C.2.6.1 Tests should be carried out on each valve in all positions in which it is intended to be used. Qualitative and quantitative assessments should be made. Valves should be tested in all configurations defined in Table C.2 and/or Table C.3.

C.2.6.2 Pressure difference should be measured at four simulated cardiac outputs between 2 l/min and 7 l/min (e.g. 2 l/min; 3,5 l/min; 5 l/min; 7 l/min), at a single simulated normal heart rate (e.g. 70 cycles/min, systolic duration of 35 %), or as appropriate for the intended device application in accordance with ISO 5840-1:2021, Tables 3 and 4. See ISO 5840-1:2021, Annex E for guidelines regarding suggested test conditions for the paediatric population.

C.2.6.3 Regurgitant volumes should be measured at test conditions listed in Table C.4, or as appropriate for the intended device application in accordance with ISO 5840-1:2021, Tables 3 and 4. See ISO 5840-1:2021, Annex E for guidelines regarding suggested test conditions for the paediatric population.

Table C.4 — Regurgitant volume test conditions

Beat rate cycles/min	Systolic duration %	Cardiac output l/min	Pressure conditions
45	30	5	Hypotensive, normotensive, severe hypertensive
70	35	5	Hypotensive, normotensive, severe hypertensive
120	50	5	Hypotensive, normotensive, severe hypertensive

C.2.7 Test procedure

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

a) mean pressure difference across the test heart valve substitute;

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

c) forward flow volume;

d) cycle rate;

e) mean arterial pressure over the whole cycle;

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

g) regurgitant volume, including the closing volume and leakage volume (see ISO 5840-1:2021, Figure 2), expressed in millilitres and as a percentage of forward flow volume; and the corresponding mean back pressure across the closed valve.

C.2.8 Test report

The pulsatile-flow test report should include:

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

b) a description of the pulse duplicator, as specified in C.2.3, and its major components and associated apparatus, including a schematic diagram of the system giving the relevant chamber dimensions and valve orientation, chamber compliance (if a compliant chamber is used), details of the location of the pressure-measuring sites relative to the base of the leaflets of the heart valve substitute, pressure measurement instrumentation frequency response, and the appropriate representative pressure and flow waveforms at nominal conditions for a healthy normal adult; see ISO 5840-1:2021, Annex E for paediatric parameters);

c) an assessment, including appropriate documentation, of the opening and closing action including leaflet kinematics of a test heart valve substitute;

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

   1) simulated cardiac output;

   2) cycle rate;

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

4) forward flow volume;

5) mean and RMS flow rates;

6) mean pressure difference;

7) effective orifice area;

8) regurgitant volume and closing volume and leakage volume, expressed in millilitres and as a percentage of forward flow volume; and the corresponding mean back pressure;

9) mean arterial pressure over the whole cycle;

e) photographic and/or videographic documentation and analyses of the opening and closing characteristics for the heart valve substitute;

f) results of reference valve testing, to demonstrate appropriate functioning of pulse duplicator system.

Annex D
(normative)

Requirements for delivery system design and evaluation

D.1 General

ISO 25539-1 and ISO 10555-1 were used as a basis for defining delivery system design evaluation requirements specified herein. Relevant clauses of IEC 62366-1 can also apply. For delivery systems with electrical power, requirements of the IEC 60601-1 series 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).

D.2 Implant interactions with delivery system

The manufacturer shall evaluate interactions between the implant and delivery system during use in accordance with the product specification to ensure no damage is induced to the implant or delivery system. In addition to visual assessment of acute damage, the impact of the interaction with the delivery system on valve durability shall be assessed as defined in 7.2.5.2. The following aspects shall be evaluated as applicable:

— crimping/loading and attachment of the device to the delivery system;

— loading device into the delivery sheath;

— positioning/deployment of the device within the target implant site;

— repositioning/recapturing of the device (if applicable) including damage to the valve;

— withdrawal of the delivery system;

— compatibility with ancillary devices.

D.3 Loading of the device into/onto the delivery system

The manufacturer shall define all specific performance parameters to be evaluated to verify consistent, safe and reliable loading of the device into/onto the delivery system. The manufacturer shall demonstrate that the implantable device can be reliably attached to the delivery system in accordance with the product specification and satisfy attachment performance requirements, such as:

— attachment strength between the device and the delivery system;

— no damage to the device or the delivery system;

— loaded/ crimped diameter;

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

— proper orientation of the device into the delivery system;

— dislodgement force;

— device sterility;

— device rinsing;

— delivery system flushing (de-airing).

D.4 Ability to access and deploy

The manufacturer shall demonstrate that the attachment between the device and the delivery system is sufficient to permit safe, repeatable and reliable delivery of the device to the intended implant site (e.g. native valve or pre-existing prosthetic device), release of the device from the delivery system and safe removal of the delivery system from the patient in accordance with the product specification. 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 (operator interface);

— method of insertion and force of insertion (impact on anatomy);

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

— flex/kink resistance;

— bond strength (tensile and torque);

— torquability;

— pushability;

— trackability;

— access angle between the delivery system and the annular plane for trans-apical delivery approach;

— compatibility with anatomical considerations depending on delivery approach;

— haemostasis;

— time to deploy, including time of flow restriction or blockage, time to restore flow and effect on crimped device;

— remodelling of surrounding anatomical structures (e.g. transseptal puncture site);

— balloon characteristics (if applicable):

  — inflation/deflation time;

  — relationship between the implant diameter and balloon inflation pressure, including assessment of effects associated with over-inflation and under-inflation;

  — relationship between the implant site compliance and balloon inflation pressure, with particular consideration of effects of pre-existing prostheses for ViV and ViR indications;

  — mean burst pressure;

  — rated burst pressure;

  — rated fatigue.

Annex E
(informative)

Examples of design specific testing

E.1 Stent creep

An assessment of the potential for structural creep (e.g. polymeric frames) of the transcatheter heart valve substitute and its structural components should be performed in order to evaluate the risk associated with potential hazards that may be, fully or in part, related to cyclic creep of the frame.

E.2 Environmental degradation

The degradation resistance of all materials including potential particulate generation (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.

E.3 Static pressure; "burst" test

A measurement of the hydrostatic load that results in cusp prolapse or tear should be conducted.

E.4 Calcification

A measurement of the rate and degree of calcification of the transcatheter heart valve substitute using *in vivo* or *in vitro* models should be considered.

E.5 Particulate generation

An assessment of the number and sizes of the particulates generated during device delivery, deployment, recapture, if applicable, and removal in a simulated use model should be conducted.

E.6 Effects of device post-dilatation

An assessment of the effects of post-implant dilatation on the leaflets and frame should be conducted if this is an expected use condition to which the heart valve substitute will be exposed.

E.7 Expansion uniformity

An assessment of the unintended frame expansion non-uniformity in a simulated use model and its potential impact on hydrodynamic performance should be conducted.

E.8 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 PVL) should be conducted.

E.9 Intentional cracking of a pre-existing prosthesis

An assessment of the impact of intentionally cracking a pre-existing prosthesis before, during or after transcatheter valve deployment on device safety and performance should be conducted, if applicable.

Annex F
(informative)

Preclinical *in vivo* evaluation

F.1 General

Based on the risk management assessment and in order to predict the safety and performance of clinical use, the study should be designed to provide a sufficient number of animals implanted with transcatheter heart valve substitutes and control valve substitutes. The rationale for animal models and justification for the use of alternative anatomical sites and implantation methods should be provided.

Evaluations listed in Table F.1 are not intended as mandatory or all-inclusive. Each of the described evaluations includes the minimum parameters necessary to assess a specific issue. However, additional parameters might be relevant depending on specific study goals and/or manufacturer product claims. Acute testing of transcatheter heart valve substitutes can be performed under non-sterile conditions.

Table F.1 — Examples of evaluations

Evaluation	Acute	Chronic
Haemodynamic performance	X	X
Ease of use	X	X
Device migration/embolization	X	X
Interference with adjacent anatomical structures	X	X
Haemolysis		X
Thrombo-embolic complications	X	X
Calcification/mineralization		X
Pannus formation/tissue ingrowth/foreign body response		X
Structural valve deterioration and non-structural valve dysfunction		X
Assessment of valve and non-valve related pathology		X

F.2 Disposition of evaluations

F.2.1 General

The evaluations listed in Table F.1 can be addressed as follows.

F.2.2 Haemodynamic performance

Transvalvular mean pressure differential and regurgitation should be measured, at least on the day of elective euthanasia, at cardiac outputs across the range of 2,5 l/min to 6 l/min. Transvalvular regurgitation, including PVL measurement should be performed using a continuous flow measurement technique or other methods which do not require crossing 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.

F.2.3 Ease of use

The ease of use should include a descriptive acute assessment and chronic assessment of the handling characteristics of the transcatheter heart valve substitute 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, balloon valvuloplasty) should be described. Visualization of valve function and alignment should be performed intra- and post-operatively using appropriate imaging modalities. The performance characteristics of the selected equipment should be documented.

F.2.4 Device migration or embolization

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

F.2.5 Interference with or damage to adjacent anatomical structures

Interference with coronary ostia, cardiac conduction system, native valve structures, aorta, myocardium should be assessed and documented as appropriate.

F.2.6 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.

F.2.7 Thrombo-embolic events

Thrombo-emboli should be evaluated in terms of macroscopic description, photographic documentation and a histologic description of the thrombotic material. A full post-mortem examination should be performed to disclose peripheral thrombo-emboli, both macro- and microscopically. Thrombo-emboli could originate from the access site, implant site, adjacent cardiac chamber, delivery system or heart valve substitute.

F.2.8 Calcification/mineralization

Calcification/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 valve.

F.2.9 Pannus formation/tissue ingrowth

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

F.2.10 Structural valve deterioration and non-structural dysfunction

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