भारतीय मानक
Indian Standard

IS 17840 (Part 2) : 2022
ISO 5840-2 : 2021
[*Superseding* IS/ISO 5840-2 : 2015]

कार्डियोवैस्कुलर अंतररोपण — कार्डियक वाल्व प्रोस्थेसिस

भाग 2 सर्जिकल रूप से प्रत्यारोपित हृदय वाल्व विकल्प

(पहला पुनरीक्षण)

Cardiovascular Implants — Cardiac Valve Prostheses

Part 2 Surgically Implanted Heart Valve Substitute

(First Revision)

ICS 11.040.40

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NATIONAL FOREWORD

This Indian Standard (Part 2) (First Revision) which is identical with ISO 5840-2 : 2021 'Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitute' issued by the International Organization for Standardization (ISO) was adopted by the Bureau of Indian Standards on recommendation of the Thoracic and Cardiovascular Surgery Instruments Sectional Committee and approval of the Medical Equipment and Hospital Planning Division Council.

This standard supersedes IS/ISO 5840-2 : 2015 'Cardiovascular implants — Cardiac valve prostheses: Part 2 Surgically implanted heart valve substitutes.

This Indian Standard is published in three parts. The other parts in this series are:

Part 1 General Requirements

Part 3 Heart Valve Substitutes Implanted by Transcatheter Techniques

The text of ISO Standard has been approved as suitable for publication as an Indian Standard without deviations. Certain terminologies and conventions are, however, not identical to those used in Indian Standards. Attention is particularly drawn to the following:

a) Wherever the words 'International Standard' appear referring to this standard, they should be read as 'Indian Standard'.

b) Comma (,) has been used as a decimal marker, while in Indian Standards, the current practice is to use a point (.) as the decimal marker.

In this adopted standard, reference appears to certain International Standards for which Indian Standards also exist. The corresponding Indian Standards, which are to be substituted in their respective places, are listed below along with their degree of equivalence for the editions indicated:

International Standard	*Corresponding Indian Standard*	*Degree of Equivalence*
ISO 5840-1 : 2021 Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements	IS 17840 (Part 1) : 2022/ISO 5840-1 : 2021 Cardiovascular implants — Cardiac valve prostheses: Part 1 General requirements	Identical
ISO 5840-3 Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques	IS 17840 (Part 3) : 2022/ISO 5840-3 : 2021 Cardiovascular implants — Cardiac valve prostheses: Part 3 Heart valve substitutes implanted by transcatheter techniques (*first revision*)	Identical

The technical committee has reviewed the provisions of the following International Standards referred in this adopted standard and has decided that they are acceptable for use in conjunction with this standard:

International Standard	*Title*
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 16061	Instrumentation for use in association with non-active surgical implants — General requirements

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Introduction

This document has been prepared for surgical 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 5840-3.

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Indian Standard

CARDIOVASCULAR IMPLANTS — CARDIAC VALVE PROSTHESES

PART 2 SURGICALLY IMPLANTED HEART VALVE SUBSTITUTE

(First Revision)

1 Scope

This document is applicable to heart valve substitutes intended for implantation in human hearts, generally requiring cardiopulmonary bypass and generally with direct visualization. See Annex E for examples of surgical heart valve substitutes and their components.

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

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

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

For some heart valve substitutes (e.g. sutureless), the requirements of both this document and ISO 5840-3:2021 can be relevant and are considered as applicable to the specific device design and are based on the results of the risk analysis.

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 5840-3, *Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques*

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 16061, *Instrumentation for use in association with non-active surgical implants — General requirements*

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 shall 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
component-joining material
material such as a suture, adhesive, or welding compound used to assemble the components of a heart valve system

[SOURCE: ISO 5840-1:2021, 3.31]

3.4
external sewing ring diameter
ESRD
outside diameter in millimetres of the sewing ring at the largest point

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.5, 3.7 and 3.8.

3.5
prosthesis minimum internal diameter
<flexible surgical heart valve> numerical indication of the minimum diameter within a fully assembled flexible surgical heart valve substitute and which is measured with a standard validated procedure, taking the entire flow channel into consideration

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2 and 3.4.

3.6
prosthesis minimum internal diameter
<rigid surgical heart valve> measurement of the prosthesis minimum internal housing diameter

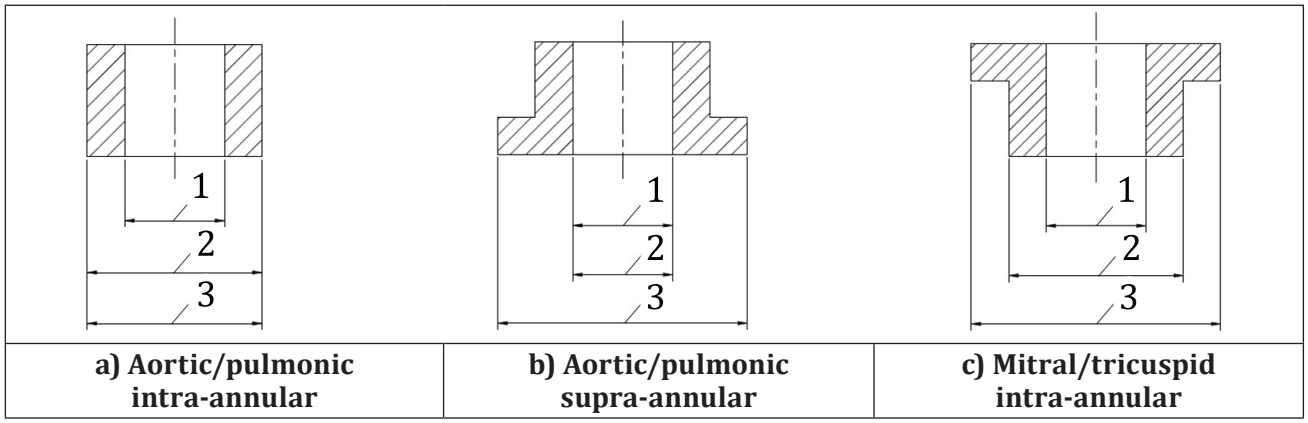
Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2 and 3.4.

3.7
intra-annular
wholly or partially within the patient's annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.4, 3.5 and 3.8.



a) Aortic/pulmonic intra-annular	b) Aortic/pulmonic supra-annular	c) Mitral/tricuspid intra-annular

Key

1 prosthesis minimum internal diameter

2 patient annulus diameter

3 external sewing ring diameter

Figure 1 — Designation of dimensions of surgical heart valve substitute sewing ring configurations

3.8
supra-annulus
region wholly above the patient's annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.4, 3.5, and 3.7.

3.9
patient annulus diameter
PAD
diameter in millimetres of the smallest flow area within the patient's valve annulus

Note 1 to entry: See Figure 1.

3.10
valve size
designated valve size
manufacturer's designation of a surgical heart valve substitute which indicates the intended patient annulus diameter

Note 1 to entry: The valve size is equivalent to the *PAD* (3.9).

Note 2 to entry: This takes into consideration the manufacturer's recommended implant position relative to the annulus and the suture technique.

4 Abbreviations

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

AE adverse event

CIP clinical investigation plan

CRF case report form

CT computed tomography

EOA effective orifice area

FEA finite element analysis

IFU instructions for use

LVOT left ventricular outflow tract

MRI magnetic resonance imaging

OPC objective performance criteria

PMCF post-market clinical follow-up

PVL paravalvular leak

RMS root mean square

SAE serious adverse event

TEE transoesophageal echo

TTE transthoracic echo

5 Fundamental requirements

Refer to ISO 5840-1:2021, Clause 5.

6 Device description

6.1 General

Refer to ISO 5840-1:2021, 6.1.

6.2 Intended use

Refer to ISO 5840-1:2021, 6.2.

6.3 Design inputs

6.3.1 Operational specifications

Refer to ISO 5840-1:2021, 6.3.1.

6.3.2 Performance specifications

6.3.2.1 General

Refer to ISO 5840-1:2021, 6.1 for general requirements.

6.3.2.2 Surgical heart valve substitute minimum performance requirements

Surgical heart valves shall meet the following minimum performance specifications:

— allow forward flow with acceptably small mean pressure difference;

— prevent retrograde flow with acceptably small regurgitation;

— resist embolization;

— avoid haemolysis;

— resist thrombus formation;

— be biocompatible;

— be compatible with *in vivo* diagnostic techniques;

— be deliverable and implantable in the target population;

— be able to ensure effective fixation within the target implant site;

— have an acceptable noise level;

— have reproducible function;

— maintain structural and functional integrity during the expected lifetime of the device;

— maintain its functionality and sterility for a reasonable shelf life prior to implantation.

6.3.2.3 Accessories

The requirements of ISO 16061 for instruments used with surgical implants shall apply. Surgical heart valve accessories shall mitigate the risk of the valve being inadvertently implanted upside down.

Examples of surgical valve accessories, including sizing tools and valve handles, are shown in Annex E.

6.3.2.4 Implant procedure

Refer to ISO 5840-1:2021, 6.3.3.

6.3.3 Packaging, labelling, and sterilization

Refer to ISO 5840-1:2021, 6.3.4.

In addition to the items specified in ISO 5840-1:2021, C.1.3, outer container labelling for the valve implant shall include in diagrammatic and/or tabular form the following items:

— intended valve to be replaced;

— intended position in relation to the annulus;

— inflow internal orifice diameter;

— prosthesis minimum internal diameter;

— external sewing ring diameter (ESRD).

Annex D contains a list of terms that may be used in describing various valve models.

6.4 Design outputs

Refer to ISO 5840-1:2021, 6.4.

6.5 Design transfer (manufacturing verification/validation)

Refer to ISO 5840-1:2021, 6.5.

6.6 Risk management

Refer to ISO 5840-1:2021, 6.6.

Annex A contains a list of potential hazards specific to surgical 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 surgical heart valve substitutes are provided in this document.

7.2 *In vitro* assessment

7.2.1 General

Refer to ISO 5840-1:2021, 7.2.1.

7.2.2 Test conditions, sample selection, and reporting requirements

Refer to ISO 5840-1:2021, 7.2.2.

7.2.3 Material property assessment

Refer to ISO 5840-1:2021, 7.2.3.

7.2.4 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid dynamic performance of the surgical heart valve substitute. ISO 5840-1:2021, Annex I provides guidelines for conducting and reporting steady hydrodynamic tests. Guidelines for conducting and reporting of pulsatile hydrodynamic tests are provided in Annex F. For pulsatile flow testing, the performance of the pulse duplicator shall be characterized. Refer to F.2.2.2 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 [11] provides characteristics of reasonable aortic and mitral waveforms.

Tests shall be carried out on at least three surgical heart valve substitutes of each size and on at least one reference valve of each of the smallest, largest, and an intermediate size. A larger sample size may be required to ensure adequate representation of the expected variability in the manufacture of devices.

The *in vitro* test results shall meet or exceed the minimum performance requirements provided in Table 1 and Table 2, which are given as a function of valve size. The minimum performance requirements 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 pressure 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). The minimum performance requirements are based on values in the published scientific literature. The values in Table 1 and Table 2 are applicable to new or modified heart valve substitutes which have not been clinically proven or evaluated under previous versions of the ISO 5840 series.

For pulmonary and tricuspid heart valve substitutes and paediatric devices, minimum performance requirements are not provided; however, the manufacturer shall justify the acceptability of hydrodynamic performance of the devices.

Additional hydrodynamic characterization testing shall be conducted over a range of test conditions as described in Annex F, F.2.3.2 and F.2.3.3. This testing is for characterization purposes only without corresponding minimum performance requirements.

Table 1 — Minimum device performance requirements, aortic

Parameter	Valve size 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
Total regurgitant fraction (% of forward flow volume) less than or equal to	10	10	10	10	15	15	20	20

Table 2 — Minimum device performance requirements, mitral

Parameter	Valve size mm					
	23	25	27	29	31	33
EOA (cm^2) greater than or equal to	1,05	1,25	1,45	1,65	1,90	2,15
Total regurgitant fraction (% of forward flow volume) less than or equal to	15	15	15	20	20	20

The total regurgitant fraction shall include closing volume and leakage volume (see ISO 5840-1:2021, Figure 2). For traditional surgical valve designs with a sewing ring, the ring fabric may be sealed to prevent paravalvular leakage during testing. For novel surgical valve designs without a sewing ring (e.g. sutureless), sealing shall be justified and paravalvular leakage volume shall be included in the leakage volume.

7.2.5 Structural performance assessment

7.2.5.1 General

An assessment of the ability of the surgical heart valve substitute to withstand the loads and/or deformations to which it will be subjected shall be performed in order to evaluate the risks associated with potential structural failure modes.

7.2.5.2 Implant durability assessment

The requirements of ISO 5840-1 shall apply.

7.2.5.3 Device structural component fatigue assessment

The requirements of Annex H and of ISO 5840-1 shall apply.

7.2.5.4 Component corrosion assessment

The requirements of ISO 5840-1 shall apply.

7.2.5.5 Cavitation (rigid valves)

An assessment of the potential for cavitation as indicated by the formation of vapor bubbles during valve closure shall be considered for rigid valves. Assessment of cavitation damage shall be performed by a detailed examination of study valves used in the preclinical *in vivo* study and in the simulated long-

term *in vitro* study (i.e. durability assessment). The *in vitro* cavitation assessment shall be performed by characterization of the smallest and largest valve sizes in terms of any observed damage and the extent of damage compared to the appropriate reference valves.

7.2.6 Design- or procedure-specific testing

7.2.6.1 General

See Annex G for examples of design specific or procedure specific testing to be considered. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific device design.

7.2.6.2 Visibility

The ability to visualize the implanted device using the manufacturer's recommended imaging modalities (e.g. fluoroscopy, MRI, CT, echocardiography) shall be evaluated.

7.2.7 Device MRI compatibility

Refer to ISO 5840-1:2021, 7.2.7.

7.2.8 Simulated use

The requirements of ISO 5840-1:2021, 7.2.8 shall apply.

The model shall consider anatomical variation in intended patient population with respect to intended implant site as well as physiological factors (e.g. temperature effects, pulsatile flow). In the case where device anchoring relies on specific interactions with the native anatomy (e.g. annulus, aortic root), testing of the interactions shall be included in the simulated use evaluation. Justification for critical parameters of the simulated use model shall be provided.

7.2.9 Human factors/usability assessment

The requirements of ISO 5840-1:2021, 7.2.9 shall apply.

7.2.10 Implant thrombogenic and haemolytic potential assessment

The requirements of ISO 5840-1:2021, 7.2.10 shall apply.

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 devices in order to address the safety and performance of the surgical heart valve substitute. For design modifications to surgical heart valve substitutes 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 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 surgical heart valve substitute;

b) assess the surgical handling characteristics of the test surgical heart valve substitute and its accessories (if any);

c) assess the biological reaction to the surgical heart valve substitute; consideration shall be given but not limited to the following items:

   1) healing characteristics (pannus formation, tissue overgrowth);

   2) haemolysis;

   3) thrombus formation;

   4) embolization of material from the heart valve substitute;

   5) biological response (e.g. inflammation, rejection);

   6) calcification (flexible valves);

   7) acoustic characteristics (rigid valves), if the manufacturer is making specific acoustic claims;

   8) structural valve deterioration and/or non-structural valve dysfunction;

   9) cavitation (rigid valves);

d) mimic, as closely as possible, the condition of the finished product as intended for clinical use, including exposure to process chemicals and the maximum number of allowed sterilization cycles;

e) evaluate the test surgical heart valve substitute in all positions for which it is intended (e.g. aortic, mitral);

f) subject comparably sized control surgical heart valve substitutes to identical test conditions as the test surgical heart valve substitute;

g) mimic, as closely as possible, the implantation technique for the placement of both the test and the control surgical heart valve substitutes (e.g. suture technique and orientation);

h) be performed by appropriately experienced and knowledgeable test laboratories;

i) address animal welfare in accordance with the principles given 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 are given in Annex C. The intent of these studies is to mimic as closely as possible the clinical use and haemodynamic performance of the surgical heart valve substitute. It is recognized that adverse events 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, adverse clinical events arising during or after valve implantation shall be carefully analysed and interpreted in order to identify the cause of the adverse event to the extent possible.

The investigator should seek to control as many variables as possible within each study arm (e.g. species, gender, and age). The test surgical heart valve substitute shall be assessed in anatomical positions for which it is intended to be used clinically. Animals suffering from perioperative complications not related to the heart valve substitute may be excluded from the group of study animals with appropriate justification, but information about them shall be reported.

The number of animals used for implantation of test and control surgical heart valve substitutes and study endpoints shall be justified for each test based on the risk analysis.

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 days). A minimum duration less than 140 d may be suitable for evaluating minor modifications of an existing surgical 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 device related pathology. The report shall include this information from all animals that have been entered into the study.

The study shall provide at least the following:

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

b) any detectable pathological consequences involving the surgical heart valve substitute and/or the major organs, including but not limited to: post-implantation changes in shape or structural components, thrombo-embolic phenomena, pannus formation, and inflammatory responses;

c) any detectable structural alterations (macro- or microscopic or radiographic) in the surgical heart valve substitute (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) implantation characteristics, including but not limited to usability, handling characteristics, and sizing technique;

f) haemodynamic performance over a range of cardiac indices (e.g. 2,5 l/min to 6,0 l/min);

g) any paravalvular leakage (PVL);

h) adverse clinical events, (e.g. myocardial infarction, significant cardiac arrhythmias, infection);

i) any other system or procedure related complication or events.

7.3.4 Test report

The test laboratory shall produce the test report, which shall include a summary assessment of the data generated during the course of the investigation. The test report shall include the complete study protocol. All data generated from the preclinical *in vivo* evaluation shall be incorporated into a comprehensive test report. The report should include the results generated by tests described in Annex C.

The test report shall include the following:

a) identification of each valve used (product description, serial number, and other appropriate valve 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 operative procedure, including implant technique, test surgical heart valve substitute orientation, valve position, and operative complications;

d) description of the pre-procedural and post-procedural clinical course of each animal including, clinical observations, medication(s), and interventions used to treat adverse events; a description of,

and a justification for, any anticoagulation or antiplatelet drug regimen used as well as therapeutic level monitoring methods;

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

f) names of the investigators and their institutions along with information about the implanting personnel and the laboratory's experience with surgical 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 surgical heart valve substitute under investigation;

h) for survival studies, the study pathologist's report that includes gross and radiographic examination and histopathology findings for each explanted surgical heart valve substitute, 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 (e.g. thromboembolism or any other adverse effects assumed to be caused by the heart valve substitute);

j) 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 C, 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 surgical heart valve systems and expanded indications for use. For modifications of an existing 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.

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).

Clinical investigations shall be designed to evaluate the surgical 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 surgical 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. The information derived from the pilot phase may also be used to optimize the surgical heart valve system and patient selection prior to initiation of a larger clinical investigation following further pre-clinical testing. A scientific justification shall be provided if pilot phase studies are not to be undertaken.

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 can require a head-to-head comparison with alternative treatments or standard of care;

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

c) randomised trial results can 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.

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 of ISO 14971 shall apply.

With surgical 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 implantation;

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

f) the potential for adverse haemodynamic effect.

See Annex J 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 (see ISO 5840-1:2021, Annex G). 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. 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 [9]). Imaging follow-up time points shall be specified, and justified, and the follow-up should 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 J and ISO 5840-1:2021, Annex L). The CIP shall specify all anticipated study-related adverse events, including device and/or procedure-related adverse events, in accordance with Annex J 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 meet the objective performance criteria).

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)/independent medical reviewer (IMR) for evaluation of patient safety, study conduct and progress, and when appropriate, efficacy. The monitoring board is empowered to make recommendations for or against study continuation, or study modification. 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 shall 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) the consent process shall inform the subjects of the pilot phase nature of the study and alternative options including other approved devices;

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

d) a clinical events committee (CEC) should be used for adjudication of adverse events;

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

f) 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 should include safety and effectiveness such as time-related valve safety, quality of life, and symptomatic and functional status. Other tertiary or descriptive endpoints should be considered relative to the technology. Further

information for clinical investigation endpoint selection and timing for surgical heart valve systems are provided in ISO 5840-1:2021, Annex L.

7.4.4 Ethical considerations

Although novel surgical 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 shall 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 implants the new device is equally important. Relevant guidance on conflict of interest has been provided by regulatory agencies or other organizations (see Reference [8]). 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 based on national regulations and, in line with ISO 14155, shall not be so large as to encourage patients to participate.

See also 7.4.5 for additional detail for site and investigator selection considerations. Ethics Committee/ Institutional Review Board approval shall be obtained and documented 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. 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 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;

  e) expert imaging with accredited operators and facilities (see ISO 5840-1:2021, Annex G);

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

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

h) 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;

i) experience with clinical investigations;

j) acceptable results of previous regulatory inspections.

— Clinical investigators:

a) qualifications by education, training (by manufacturer or medical experts), relevant experience, and meeting all applicable regulatory requirements;

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 [6] and [8]).

7.4.6 Statistical considerations including sample size and duration

7.4.6.1 General

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) the measures that will be evaluated;

d) the expected clinical outcomes.

For pivotal studies (single-arm or concurrent control), the sample size shall be justified and shall be sufficient to enable assessment of the study safety and performance or effectiveness endpoints of the surgical 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.

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.

7.4.6.2 Objective performance criteria for established device designs

The use of objective performance criteria (OPC) is the recommended method for the statistical evaluation of adverse event data for new devices based on established device designs (see Annex I).

The sample size should be sufficient to enable assessment of the clinical performance of the surgical heart valve substitutes as well as to quantify the associated risk. A minimum of 150 patients in each valve position is required, each of whom is intended to be studied for at least one year (understanding that death occurring prior to one year is captured and included in the one-year follow-up analysis). When appropriate to the study aims, standard statistical methods should be used to calculate the minimum sample size with prior specification of the Type 1 error rate, the statistical power, and effect sizes to be detected (refer to Annex I).

The protocol shall specify the duration of the study. There shall be at least 400 patient-years of follow-up of each valve position (e.g. aortic or mitral), or 800 patient-years of follow-up for a single position valve, to assess late adverse events (e.g. thromboembolism, valve thrombosis, haemorrhage, and infective endocarditis). The patient-years criterion can be met by further pre-market follow-up of the 150 patients beyond one-year or by enrolment of additional patients. All implants shall be analysed, including those patients not surviving through the first year, and including centres with enrolment below the intended minimum.

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.

7.4.6.3 Study designs for novel devices

Novel devices include devices with characteristics (e.g. materials, flow configurations) that have never been evaluated clinically. 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 protocol shall specify the duration of the study, including the appropriate follow-up intervals and the minimum overall patient-years in consideration of Annex I. The duration depends on the risk assessment, the intended application and, if relevant, the type of device modification.

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 for guidance). If a comparable device is on the market, the study control may be the comparable device or another comparator, such as non-surgical therapy. If a comparable device is not on the market, randomisation against an appropriate comparator should be used. If the study uses a non-inferiority design, the non-inferiority margin should be justified and, to the extent feasible, based on prior data from comparable devices.

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.

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-morbid conditions (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, hematologic disorders, chronic lung disease);

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

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

i) surgical status (e.g. elective, urgent, 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.

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 data

The following data shall be collected:

a) 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 ISO 5840-1:2021, Annex G);

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

i) blood test to assess hepatic, cardiac and renal status, and including 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) medications including start/stop dates, dosage, changes, change justification (e.g. antithrombotic regimen, inotropes, antibiotic prophylaxis).

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

f) pre-op inotropic support or circulatory assist device;

g) access site and technique (e.g. sternotomy, thoracotomy);

h) bypass time, body temperature on bypass ischaemic time, type of myocardial protection;

i) imaging modalities (e.g. fluoroscopy, TEE, TTE, CT);

j) assessment of implant site and patient annulus diameter, or other relevant sizing measure of patient;

k) any changes from original diagnosis;

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

m) any concomitant interventions or procedures (e.g. coronary revascularization);

n) elements of procedure, including any adjunctive procedures performed;

o) implant position (e.g. aortic, mitral, pulmonic, tricuspid) and anatomical implant position in relation to the annulus (e.g. intra-annular, supra-annular; refer to Figure 1);

p) suture technique (e.g. continuous, interrupted, use of pledgets), if applicable;

q) size, type, implant date and failure mode of previously implanted prosthesis;

r) procedural complications, including acute interventions;

s) evaluation of surgical 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.

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

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

The following data shall be collected:

a) date, type (e.g. 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-minute walk test, peak VO_2);

e) device assessment (e.g. structural integrity, any thrombus deposition); see Annex J. For pilot and pivotal studies of surgical mitral valves, a TEE study shall be performed on all patients within the first four weeks to six weeks;

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 and/or anticoagulation regimen and antiarrhythmic medications) including start/stop dates, dosage, changes, change justification; it is recommended that this information also be collected on other medications;

k) adverse events as specified in Annex J

l) concomitant therapies, (e.g. cardiac assist, pacing);

m) date and reason for reintervention;

n) date and cause of death;

o) explant analysis and post-mortem examination report; 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 conform 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 (refer to Annex J, ISO 5840-1:2021, Annex G, 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 where possible. Subsequent outcomes shall be reported, including disclosure of both positive and negative results, in accordance with applicable requirements. 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 shall 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 mode of death and 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 will have been extensively studied in the pre- and peri-operative periods with full documentation, and because overall mortality and adverse event rates can be calculated. Reasons for removing individual patients from longer-term follow-up shall be documented and justified. 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 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 shall 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)

Surgical heart valve substitute hazard analysis example

A.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 surgical heart valve system. The manufacturer should consider both the indicated use and anticipated use of their device (e.g. use in alternate locations or in non-indicated age groups). Table A.1 is an example that is intended to demonstrate the linkage among potential hazards, foreseeable sequence of events, hazardous situations, and harms for surgical heart valve substitutes based on the framework provided in ISO 14971. The example shown is not intended to be all inclusive.

For some surgical heart valve designs, see also ISO 5840-3:2021 for applicable failure modes and possible evaluation methods.

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

Hazard	Foreseeable sequence of events	Hazardous situation	Harm
pressure gradient during forward flow phase	valve exhibits poor leaflet kinematics post-implant	poor leaflet kinematics result in excessive transvalvular gradient	a) dyspnoea b) heart failure
leaflet coaptation during reverse flow phase	valve exhibits insufficient leaflet coaptation post-implant	insufficient coaptation results in excessive transvalvular regurgitation	a) dyspnoea b) heart failure c) haemolysis
implantation error	unintended leaflet contact with native anatomical structures post-implant	impeded leaflet mobility creates region of valve that cannot be effectively washed out resulting in thrombus formation	a) thromboembolic events b) heart failure
		impeded leaflet mobility results in excessive transvalvular gradient	a) dyspnoea b) heart failure
	undersized valve implanted	patient-prosthesis mismatch resulting in excessive transvalvular gradient	a) dyspnoea b) heart failure
	insufficient number of sutures placed around sewing ring perimeter	sewing ring dehiscence from annulus resulting in paravalvular leakage or excessive gradient	a) dyspnoea b) heart failure c) haemolysis
valve holder retention	excessive force required to release valve holder from valve post-implantation	difficulty in releasing valve holder results in sewing ring dehiscence from annulus leading to paravalvular leakage or tissue trauma	a) annulus tissue damage b) bleeding complications c) haemolysis d) heart failure
sewing ring compliance	inadequate conformance of the sewing ring to the annulus	insufficient sealing around the sewing ring leading to excessive paravalvular leak	a) heart failure b) haemolysis

Table A.1 *(continued)*

Hazard	Foreseeable sequence of events	Hazardous situation	Harm
protruding frame edge	frame fracture after implantation resulting in a sharp edge	sharp frame edge comes into contact with the annulus	a) annular rupture b) annulus tissue damage c) bleeding complications

Annex B
(informative)

In vitro procedures for testing unstented or similar valves in compliant chambers

B.1 General

If the pressure difference and/or regurgitation is a function of the compliance of the vessel or chamber into which the valve is to be implanted (e.g. in the case of an unstented aortic valve), then the valve should be tested in compliant chambers as described in B.2. The protocols for pulsatile pressure difference, pulsatile regurgitation, and wear/durability should be amended as in B.3.

NOTE 1 These values are for compliance of the aorta and are not annulus values.

NOTE 2 See ISO 5840-1:2021, Annex E for paediatric conditions.

B.2 Compliant chamber specifications

B.2.1 When testing valves in compliant chambers, consider using two compliant chambers:

— a low compliance chamber for simulating patients with a normal aorta;

— a high compliance chamber for simulating younger patients, or patients with a hypercompliant aorta.

B.2.2 Recommended values for the compliance of aortic chambers are:

— low compliance chamber: $C = \frac{0{,}68\%}{\text{kPa}}\left(\frac{0{,}09\%}{\text{mmHg}}\right)$

— high compliance chamber: $C = \frac{2{,}40\%}{\text{kPa}}\left(\frac{0{,}32\%}{\text{mmHg}}\right)$

Other values for compliance should be justified by the manufacturer.

B.2.3 Recommended pressure ranges over which the chamber compliance (without the valve present) should be characterized, and the valves tested, include the hypotensive, normotensive, and moderate hypertensive conditions defined in ISO 5840-1:2021, Tables 3 and 4.

B.3 Test procedures using compliant chambers

B.3.1 Pulsatile-flow pressure difference

Test the valves in the low compliance chamber, under the hypo, normo, and moderate hypertensive pressure conditions as defined in ISO 5840-1:2021, Tables 3 and 4.

B.3.2 Pulsatile-flow regurgitation

B.3.2.1 Test the valves in the low compliance chamber under the hypo, normo, and moderate hypertensive pressure conditions as defined in ISO 5840-1:2021, Tables 3 and 4.

B.3.2.2 Test the valves in the high compliance chamber, under the hypo and normotensive pressure conditions as defined in ISO 5840-1:2021, Tables 3 and 4. Hypertensive conditions may be applicable for right-heart conditions.

B.3.3 Reference valves for hydrodynamic testing

One smallest and one largest currently marketed unstented valves should be used as reference valves in all testing using compliant chambers.

B.3.4 Wear/durability

The valves should be tested in the low compliance chamber.

Annex C
(informative)

Preclinical *in vivo* evaluation

C.1 General

Based on risk analysis 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 the test and control surgical heart valve substitute. The rationale for animal models and justification for the use of alternative implant positions and implantation methods should be provided.

Evaluations listed in Table C.1 are not intended as mandatory or all inclusive. Each of the described evaluations includes minimum parameters necessary to assess a specific issue. However, additional parameters might be relevant depending on specific study goals and/or manufacturer product claims.

Acute testing of surgical heart valve substitutes can be performed under nonsterile conditions.

Table C.1 — Settings that can be evaluated

Issue	Acute	Chronic	Flexible	Rigid
haemodynamic performance	X	X	X	X
usability	X	X	X	X
acoustic characteristics	X	X		X
interference with adjacent anatomical structures	X	X	X	X
haemolysis		X	X	X
thrombo-embolic complications		X	X	X
calcification/mineralization		X	X	
pannus formation/tissue ingrowth/foreign body response		X	X	X
structural valve deterioration and non-structural valve dysfunction		X	X	X
assessment of valve and non-valve related pathology		X	X	X
cavitation		X		X

C.2 Disposition of evaluations

C.2.1 General

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

C.2.2 Haemodynamic performance

Transvalvular mean pressure differential and regurgitation should be performed, at minimum on the day of elective euthanasia, at cardiac indices across a range of cardiac indices (e.g. 2,5 l/min/m^2 to 6,0 l/min/m^2). Transvalvular regurgitation 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.

C.2.3 Usability

The usability should include a descriptive acute assessment and chronic assessment of the surgical handling of the surgical heart valve substitute and accessories, if any, compared to a control including any unique features.

C.2.4 Acoustic characteristics

The acoustic characteristics of rigid surgical heart valve substitutes should be evaluated in the intended implant position. One method of accomplishing this is to use intravascular/intracardiac pressure recordings with a micro-tip pressure transducer that has an upper frequency limit no lower than 20 000 Hz. Air transmitted sound should be recorded 10 cm above the beating heart in the open chest in accordance with IEC 60651. Alternatively, the valve loudness may be directly measured by applying the Zwicker loudness measurement in accordance with ISO 532:1975, method B to valve sound recordings taken 5 cm to 10 cm above the closed chest. A technique similar to that described in Reference [7] could be used. The acoustic techniques are described in Reference [10].

C.2.5 Interference with adjacent anatomical structures

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

C.2.6 Haemolysis

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

C.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 exam should be performed to disclose peripheral thrombo-emboli both macro- and microscopically.

C.2.8 Calcification/mineralization

Calcification/mineralization should be evaluated in terms of macroscopic description, photographic, and radiographic documentation, and a histologic description of any mineral deposits. The results should be compared to a control valve.

C.2.9 Pannus formation/tissue ingrowth

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

C.2.10 Structural valve deterioration and non-structural dysfunction

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

C.2.11 Assessment of valve and non-valve related pathology

Assessment of other valve and non-valve related pathology should be macroscopically described, histologically evaluated, if appropriate, and photographically documented.

C.2.12 Cavitation

Macro- and microscopic assessment of any signs of erosion caused by cavitation should be documented.

Annex D
(informative)

Description of the surgical heart valve substitute and system

D.1 General

This annex contains a listing of terms that may be used in describing surgical heart valve system components in device documentation (e.g. labelling, IFU). The description of the surgical heart valve substitute should include, at the very least, the information listed in Table D.1. The description should be supported by pictures or illustrations where appropriate. For novel surgical heart valve substitutes, e.g. sutureless, the requirements of both this document and ISO 5840-3 can be relevant and shall be considered as applicable to the specific device design.

Table D.1 — Information to be included in the description of the surgical heart valve substitute

Major class	Subclass	Component	Implant position	Annulus position	Orientability
rigid	bileaflet tilting disc caged ball other	orifice occluder connections to annulus (e.g. sewing ring)	aortic mitral tricuspid pulmonic	supra-annular intra-annular	rotatable non-rotatable
flexible	stented unstented subcoronary full root scalloped	leaflets support structure (e.g. stents) Connections to annulus (e.g. sewing ring)	aortic mitral tricuspid pulmonic	supra-annular intra-annular	rotatable non-rotatable

EXAMPLE 1 Rigid, tilting disc, pyrolytic carbon occluder with 6–4 titanium orifice, PET/PTFE sewing ring, aortic and mitral, supra-annular, rotatable.

EXAMPLE 2 Flexible, stented, bovine pericardial, acetyl copolymer stent, PET/PTFE sewing ring, aortic and mitral, supra-annular, non-rotatable.

D.2 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.

For device-drug combination products, elements of ISO 12417-1:2015 might be applicable.

D.3 Component description

D.3.1 General

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

D.3.2 Examples of components of some surgical heart valve substitutes

The following is a listing of examples of typical valve components of some surgical heart valve substitutes. The following listing is not meant to be exhaustive:

— coating: any thin-film material that is applied to an element of a surgical heart valve substitute in order to modify its physical or chemical properties;

— component-joining material: material, such as a suture, adhesive, or welding compound, used to assemble the components of a surgical heart valve substitute, thereby becoming part of the implant device (see Figures E.1, E.2, E.3, E.4, E.5, E.6, and E.8);

— covering: any element applied to enclose any other element of the surgical heart valve substitute (see Figures E.1, E.3, E.4, E.5, E.6, and E.8);

— occluder/leaflet: component that inhibits backflow (see Figures E.1, E.2, E.3, E.4, E.5, E.6, E.7 and E.8);

— occluder retention mechanism: component(s) of a surgical heart valve substitute which support(s) or retain(s) the occluder(s) (see Figures E.1 and E.2);

— orifice ring (also housing): component of a surgical heart valve substitute that houses the occluder(s) of a rigid surgical heart valve (see Figure E.1);

— sewing ring (also sewing cuff): component of a surgical heart valve substitute by which it can be attached to the heart (see Figures E.1 and E.5);

— sewing-ring filler: any material within the confines of the sewing ring of the surgical heart valve substitute which provides it with bulk and shape (see Figure E.1);

— sewing-ring retaining material: material used to prevent separation of the sewing ring from the orifice ring or frame (see Figures E.1 and E.2);

— stent (also frame, body): component of a surgical heart valve substitute that houses the occluder(s) of a flexible leaflet device (see Figures E.5, E.6, and E.8);

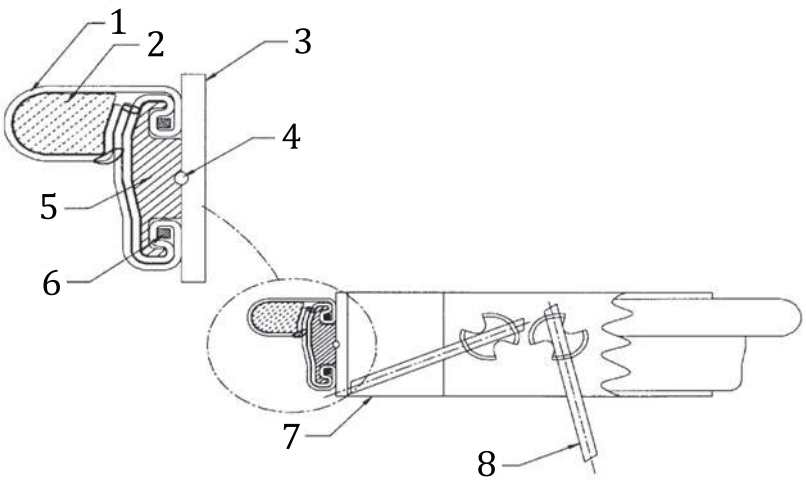
— stiffening element: component which reduces deformation of the orifice ring or stent (see Figure E.1).

D.4 Accessories

Any accessories that are to be used in conjunction with the surgical heart valve substitute and its implantation (e.g. sizers, holders, loading tools, delivery systems) should be described and their materials of construction should be provided. Double-ended sizer configurations are recommended, with a replica of the valve shape and dimensions on one end and a cylinder to measure the PAD on the other end (see Figure E.9).

Annex E
(informative)

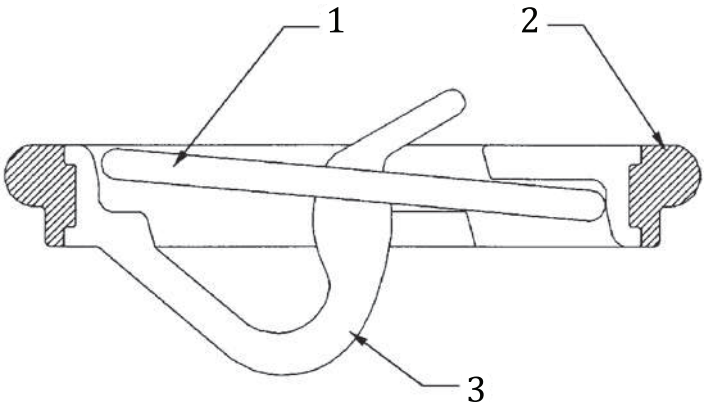
Examples of components of some surgical heart valve substitutes and systems



Key

1 covering
2 sewing ring filler
3 orifice ring
4 component joining material
5 stiffening element
6 sewing ring retaining material
7 housing
8 occluder

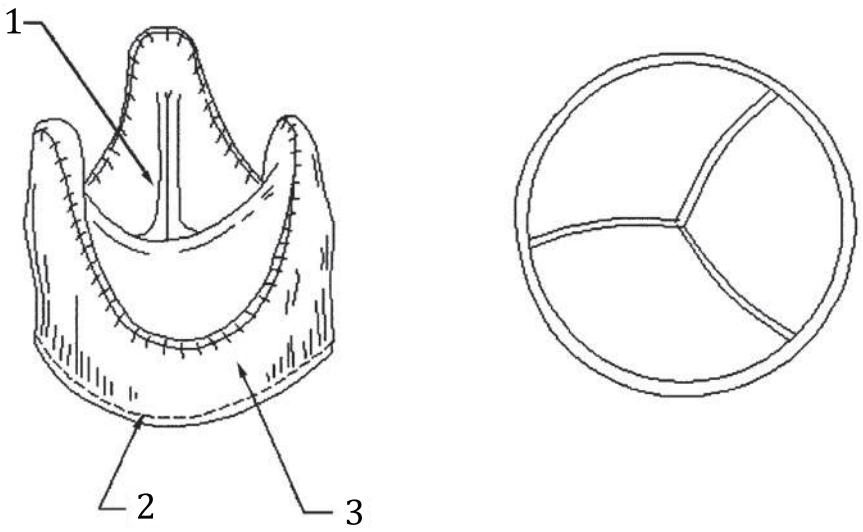
Figure E.1 — Generic bi-leaflet rigid surgical heart valve substitute



Key

1 occluder
2 sewing ring retaining material
3 occluder retention mechanism

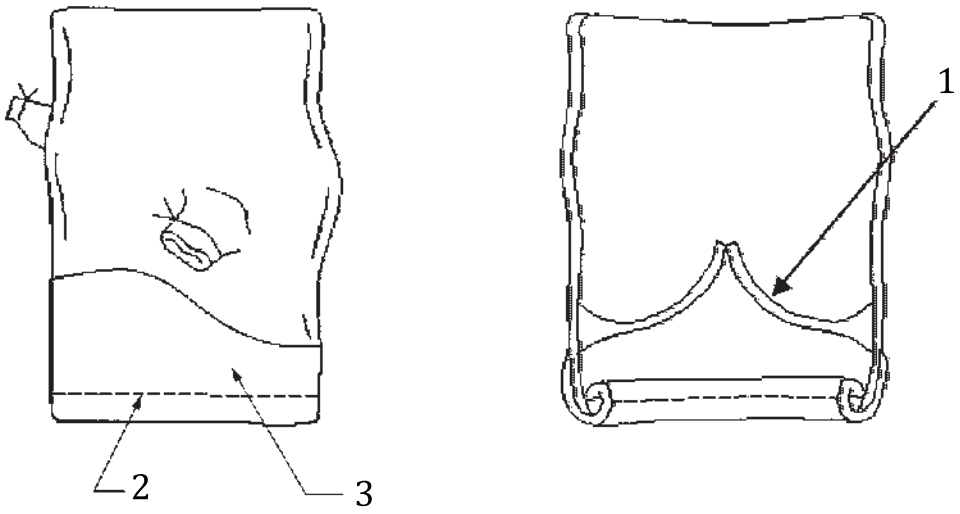
Figure E.2 — Generic mono-leaflet rigid surgical heart valve substitute



Key

1 leaflet
2 component joining material
3 covering

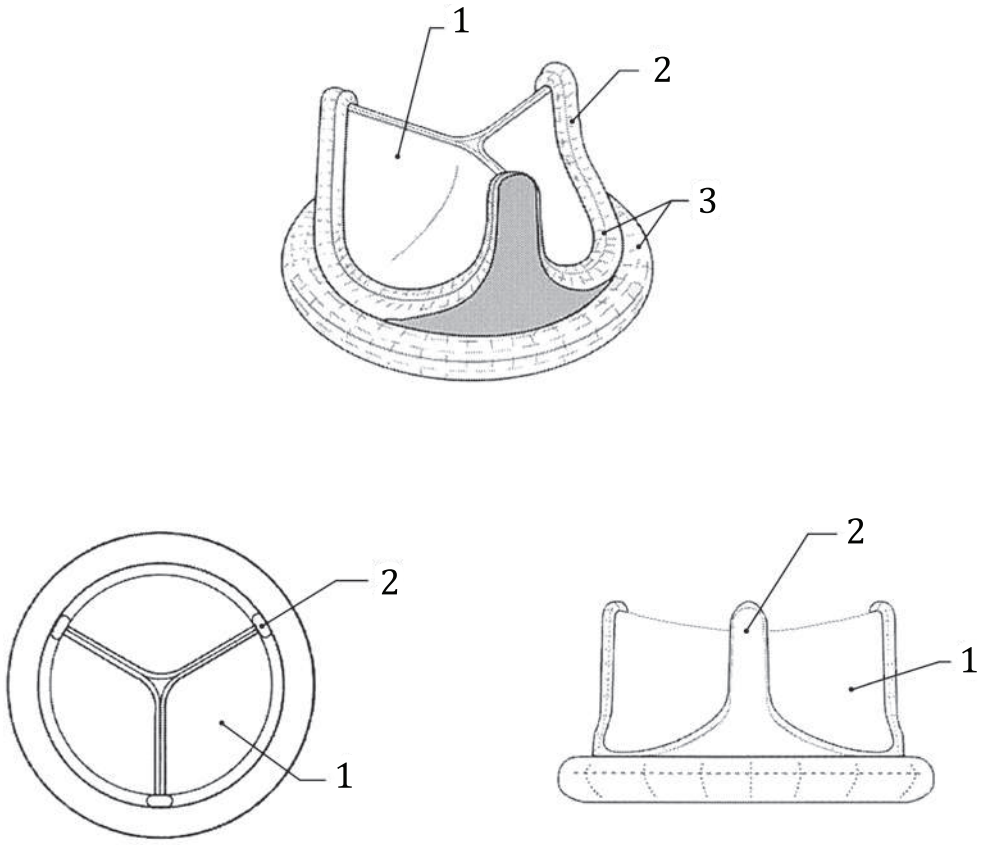
Figure E.3 — Generic flexible surgical heart valve substitute (flexible, unstented, scalloped)



Key

1 leaflet
2 component joining material
3 covering

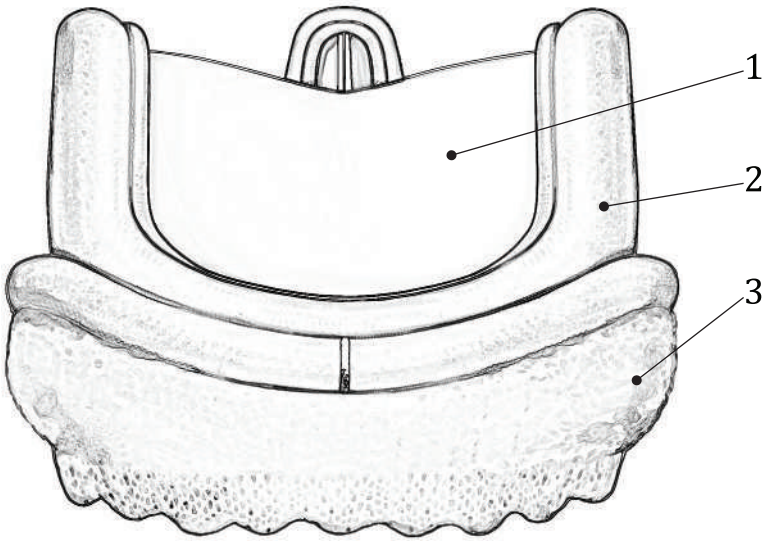
Figure E.4 — Generic flexible surgical heart valve substitute (flexible, unstented, full root)



Key

1 leaflet
2 stent
3 covering

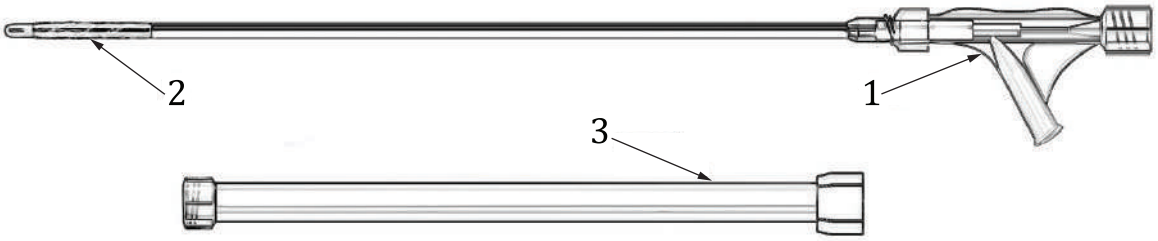
Figure E.5 — Generic flexible stented surgical heart valve substitute



Key

1 leaflet
2 stent
3 anchoring stent

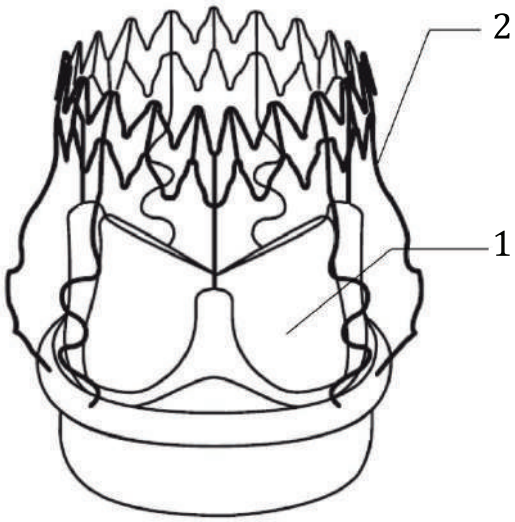
Figure E.6 — Generic surgical valve substitute, e.g. sutureless



Key

1 delivery system
2 balloon
3 delivery sheath

Figure E.7 — Generic balloon expandable rapid deployment surgical heart valve system



Key

1 leaflet

2 anchoring stent

Figure E.8 — Generic self-expanding sutureless surgical heart valve

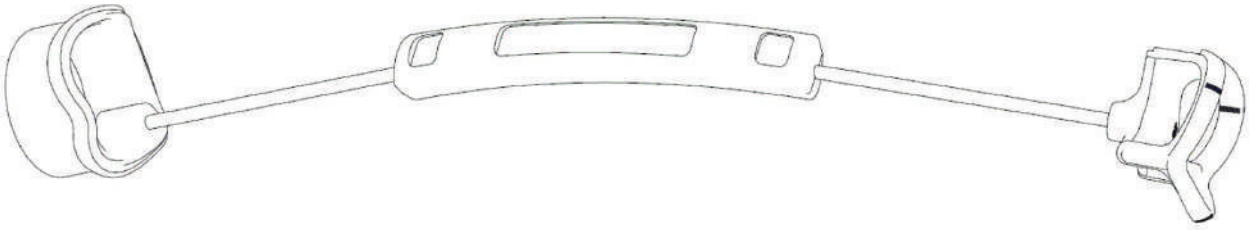


Figure E.9 — Generic double-ended sizer for a surgical heart valve

Annex F
(informative)

Guidelines for verification of hydrodynamic performance — Pulsatile flow testing

F.1 General

This annex provides guidance on test equipment, test equipment validation, formulation of test methods, and test reports for the pulsatile flow measurements of surgical heart valves.

F.2 Pulsatile-flow testing

F.2.1 Measuring equipment accuracy

F.2.1.1 The pressure measurement system should have an upper frequency limit (−3 dB cut-off) of at least 30 Hz and a differential measurement accuracy of at least ±0,26 kPa (±2 mmHg). The flow meter should have an upper frequency limit (−3 dB cut-off) of at least 30 Hz.

F.2.1.2 Regurgitant volume measurements should have a measurement accuracy of at least ±2 ml.

F.2.1.3 All other measurement equipment should have a measurement accuracy of at least ±5 % of the maximum intended test measurement.

F.2.2 Test apparatus requirements

F.2.2.1 Pulsatile-flow testing should be conducted in a pulse duplicator that 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 for guidelines regarding suggested test conditions for the paediatric population.

F.2.2.2 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 F.1 and may be used as a reference for performance characterization of a pulse duplicator. See Reference [11] for additional details. It is recommended that manufacturers utilize mechanical valve types used for the round robin study (see Reference [11] for additional details and results summarized in Table F.1) to characterize the pulse duplicator system performance.

Table F.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)	Regurgitation 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 tests are conducted at a mean arterial pressure of 100 mmHg.

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

NOTE 2 The following St. Jude Medical Masters Series mechanical valve model numbers represent different sewing ring configurations; however, the pyrolytic carbon valves assembly is the same for all model numbers for a given size and would provide similar hydrodynamic performance.

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

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

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

F.2.2.3 The pulse duplicator should permit measurement of time-dependent pressures, volumetric flow rates, velocity fields, and turbulent shear stress fields.

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

F.2.2.5 Relevant dimensions of the cardiac chambers and vessels should be simulated.

F.2.2.6 In cases where the compliance may affect the pressure difference or regurgitation characteristics of the valve (e.g. the aortic compliance in an unstented aortic valve), the relevant chamber compliance should be simulated (see Annex B for guidelines on compliant chambers).

F.2.2.7 The chamber should allow the observer to view and photograph the surgical heart valve substitute at all stages of the cycle.

F.2.3 Test procedure

F.2.3.1 Tests should be carried out on each valve in the position in which it is intended to be used. Qualitative and quantitative assessments should be made.

F.2.3.2 Pressure difference should be measured at four simulated cardiac outputs between 2 l/min and 7 l/min (e.g. 2,0 l/min, 3,5 l/min, 5,0 l/min, 7,0 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.

F.2.3.3 Regurgitant volumes should be measured in accordance with the parameters listed in Table F.2 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 in for guidelines regarding suggested test conditions for the paediatric population.

Table F.2 — 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

F.2.3.4 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 surgical heart valve substitute;

b) mean and root mean square, RMS, flow rates through the surgical heart valve substitute;

c) forward flow volume;

d) beat rate;

e) mean arterial pressure over the whole cycle;

f) systolic duration;

g) regurgitant volume, including the closing volume and leakage volume (see ISO 5840-1:2021, Figure 1), and the corresponding mean back pressure across the closed valve.

F.2.4 Test report

The pulsatile flow test report should include the following information:

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) description of the pulse duplicator, as specified in F.2.2, 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 mid-plane of the surgical heart valve substitute sewing ring, pressure measurement instrumentation frequency response, and the appropriate representative pressure and flow waveforms at nominal flow conditions;

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

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

   1) simulated cardiac output;

   2) beat rate;

   3) systolic duration;

4) forward flow volume;

5) mean and RMS flow rates;

6) mean pressure difference;

7) effective orifice area;

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

9) mean arterial pressure over the whole cycle;

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

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

Annex G
(informative)

Examples of design specific testing

G.1 Sewing ring integrity

A measure of the resistance to sewing ring dehiscence. Dehiscence may result from suture failure, suture retention failure, fabric tensile strength failure, fabric weave failure, or fabric seam failure.

G.2 Stent creep

An assessment of the potential for structural creep, e.g. polymeric stents, of the surgical 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 stent creep.

G.3 Environmental degradation

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

G.4 Static pressure; "burst" test

A measurement of the hydrostatic load at which failure, e.g. leaflet or orifice fracture or leaflet escape, occurs. For a flexible valve, failure could result in cusp prolapse or tear.

G.5 Calcification (flexible valve)

A measurement of the rate and degree of calcification of the surgical heart valve substitute using *in vivo* or *in vitro* models.

G.6 Particulate generation

An assessment of the number and sizes of the particulates generated during device delivery in a simulated use model should be conducted.

G.7 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 (novel) heart valve substitute will be exposed.

G.8 Leaflet impingement force (rigid valves)

Determination of the maximum radial compressive force (annular load) that can be applied to the valve housing before the housing distorts sufficiently to produce leaflet impingement. Evaluation should consider engineering tolerances of the component features and assembly tolerances. The timing of annular loads and position of the occluder should be considered in the evaluation.

G.9 Leaflet escape force (rigid valves)

Determination of the maximum radial compressive force that can be applied to the valve housing before the housing distorts sufficiently to allow leaflet escape. Evaluation should consider engineering tolerances of the component features and assembly tolerances. The timing of annular loads and position of the occluder should be considered in the evaluation.

G.10 Sewing ring push-off

A measurement of the strength of the sewing ring attachment to the surgical heart valve substitute.

Particular attention should be paid to the potential for the attachment mechanism to be damaged during implantation.

G.11 Sewing ring torque (rigid valves)

A measurement of the torque required to rotate the valve within the sewing ring.

G.12 Device migration resistance

The ability of the implantable device to remain in the target implant site under simulated operating conditions. See ISO 5840-3.

Annex H
(informative)

Fatigue assessment

H.1 General

See ISO 5840-1:2021, Annex K for guidance on fatigue assessment of heart valves. This annex provides additional information regarding damage tolerance assessments which may be applicable to surgical heart valves. A damage tolerance-based fatigue lifetime assessment consists of the following:

a) stress or strain analysis of the components/valve under simulated *in vivo* loading conditions; at a minimum, moderate hypertensive pressure conditions and other relevant loading modes should be considered;

b) fatigue crack growth characterization testing of the structural material/component;

c) fatigue lifetime assessment of the structural component/valve.

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

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

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

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

— transient stresses occurring during opening and closing;

— radial dilatation and compression;

— torsion;

— bending;

— axial tension;

— axial compression;

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

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

An appropriate constitutive model for each material should be used in any stress/strain analysis, including time-dependent and/or nonlinear models as appropriate. Development of constitutive models or evaluation of appropriate constants for existing constitutive models should be based on testing of material that is representative of the actual structural component, including material processing and environmental exposure (e.g. sterilization).

H.2 Fatigue crack growth, da/dN, characterization

Fatigue crack growth testing is used in association with damage tolerance analyses, which employ a fatigue crack growth relation governing crack propagation from inherent flaws in the material/component. Thus, the fracture toughness and fatigue crack growth behaviour relating the rate of crack growth, da/dN, to an appropriate measure of the cycling crack driving force (commonly taken as the cyclic stress intensity factor, ΔK, although others exist and may be more appropriate depending on material) are determined for the component material.

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

Unless plane strain conditions are ensured for the test specimen, testing should be performed on specimens whose thickness is at least as thick as the actual component. While machined notches may be used to aid and control the formation of a crack, it may be necessary to pre-crack the specimen prior to generating acceptable crack growth and/or toughness data. However, care should be taken in pre-cracking so as not to overload the specimen. For some materials, such as metals, overloads can cause large compressive stresses to develop near cracks, resulting in retarded growth and non-conservative crack growth relationships. For the same reason, testing should generally be performed under an increasing crack driving force in order to mitigate potential retardation effects.

Testing should span the range of crack driving force from threshold, or minimum anticipated driving force, to near toughness in order to adequately establish and characterize the fatigue crack growth behaviour of the material. Not all materials exhibit threshold behaviour, below which no crack growth occurs. If a threshold is used in subsequent damage tolerance analyses, the manufacturer should establish and verify its existence.

H.3 Damage tolerance analysis

A damage tolerance analysis (DTA) approach is based on the premise that all materials contain defects that may eventually grow to a critical length, as defined from the fracture toughness, resulting in failure. The lifetime of a structural component based on a damage tolerance approach is the predicted duration for a minimally detected flaw to grow to failure under *in vivo* conditions. This may require the postulation of initial flaws in critical locations of a component, typically at locations of high stress, and estimates of crack driving forces associated with those locations.

Since the lifetime is a direct function of the initial flaw size, the manufacturer should demonstrate sufficient probability of detecting the minimum flaw size, through inspection and/or proof testing, with appropriate confidence.

In order to perform damage tolerance analyses from fatigue crack growth data generated from fracture specimens, simulated *in vivo* stress analyses should be coupled with fracture mechanics analyses in which validated crack driving forces associated with actual components are obtained. In some cases, more simplified but well-known driving forces may be reasonably used to approximate *in vivo* driving forces (e.g. a crack in a leaflet might be reasonably approximated by a crack in a beam experiencing an equivalent bending load). In such cases, the manufacturer should justify the approximation and include any associated uncertainty in the DTA.

The damage tolerance assessment should identify and account for effects of permissible variances such as dimensional tolerances, material property variations (particularly with respect to fracture/fatigue crack properties and their determination), variations and confidence in identifying initial flaws, and the methodologies for assuring that variances are maintained within acceptable levels.

Annex I
(normative)

Methods of evaluating clinical data against objective performance criteria

I.1 General

If objective performance criteria (OPC)-based clinical study design is employed, methods of evaluating clinical data shall include comparing all late complications to the OPC. Frequentist or Bayesian statistical methods may be used. The manufacturer is responsible for proposing and justifying the specific methodology used.

I.2 Objective performance criteria methodology

Safety can be assessed over the defined timeframe by comparing the occurrence of late (>30 d post-implant) complications to objective performance criteria, OPC. The OPC are the average rates of valve-related complications as assessed by linearized occurrence rates. The values in Table I.1 may be used in the comparison, without further justification.

Table I.1 — Objective performance criteria for surgical heart valve substitutes

Adverse event (end-point)	Bioprosthetic		Mechanical	
	Aortic	Mitral	Aortic	Mitral
Thromboembolism	1,5	1,3	1,6	2,2
valve thrombosis	0,04	0,03	0,1	0,2
major haemorrhage	0,6	0,7	1,6	1,4
major paravalvular leak	0,3	0,2	0,3	0,5
Endocarditis	0,5	0,4	0,3	0,3

NOTE Values are in a percentage per valve-year.

The data in Table I.1 were derived using the same methodology as the original OPC, an analysis of safety and effectiveness data submitted by manufacturers in pursuit of premarket approval of bioprosthetic and mechanical valves (yielding 38359 follow-up years) combined with an analysis of recent literature from 1999 to 2012 (yielding 208585 follow-up years). There was no significant heterogeneity between the two sources of data, either in methods of data collection or in complication rates. See Reference [12].

The formal statistical method applied to OPC specifies that the observed rates should be numerically less than twice the OPC.

For a single position valve, a sample size of 800 patient-years is required. If the investigational design is for use in both the aortic and mitral positions, the data shall be presented stratified. A minimum of 400 patient-years are required for each valve position; however, if possible, it is recommended that more than 400 patient-years are collected in both positions to enable more reliable comparisons to the OPC.

Assuming a one-sided type one error rate of 5 %, with 800 patient-years, only thromboembolism (all positions, both bioprosthetic and mechanical) and major haemorrhage (mechanical valves only) are likely to have at least 80 % power to satisfy the OPC described in the previous paragraph.

Annex J
(normative)

Adverse event classification during clinical investigation

J.1 General

The manufacturer shall ensure that investigators evaluate and report all adverse events (AEs), for all study subjects, from the time the subject is enrolled (after signing the informed consent form) to the end of the follow-up period. When reporting adverse events, the manufacturer should clearly identify how events are classified and reported.

J.2 Evaluation

The manufacturer shall develop systems to ensure that all adverse events and device deficiencies are received, evaluated and communicated to interested parties without unjustified delay in accordance with ISO 14155 and other applicable regulations.

J.3 Data collection requirements

The manufacturer shall ensure the following information is documented on a CRF, for all observed AEs:

— date of onset or first observation;

— description of the event;

— seriousness of the event;

— presumptive causal relationship of the event to the device, procedure or patient condition;

— treatment required;

— outcome or status of the event.

J.4 Adverse events

Each AE shall be defined and categorised as either a serious adverse event (SAE) or non-serious adverse event according to the definitions in ISO 14155:2020.

To provide context to ISO 14155 in terms of SAE definition, “life-threatening” indicates that unless a medical or surgical intervention takes place, the event is highly likely to lead to death in the near future. In this context, “intervention” includes a change in medication and percutaneous interventions.

J.5 Adverse device effects

Each adverse device effect (ADE) shall be defined and categorized as either a serious adverse device effect (SADE) or a non-serious adverse device effect in accordance with the definitions in ISO 14155:2020. Serious adverse device effects are further categorised as anticipated or unanticipated.

To provide context to ISO 14155 in terms of definition, adverse device effects are adverse events related to the use of an investigational medical device. Therefore, adverse device effects are a subset of adverse events.

J.6 Device deficiencies

Device deficiencies shall be reported as required by ISO 14155.

To provide context to ISO 14155 in terms of definition, the term device deficiency shall be used for incidences that did not result in an adverse event but have the potential to lead to an adverse event. An example of a potential device deficiency includes, but is not limited to, frame fractures.

J.7 Classification of causal relationships

After establishing that an AE has occurred, causal relationship shall be determined in reference to the device, the procedure or the patient's condition. Some events may be related to more than one category and should be reported in each category. In some cases, the AE may be caused by something other than the device, the procedure or the patient's condition.

— Device-related: any AE involving the function of the heart valve replacement system, or the presence of the device in the body. Included in this category are events that are directly attributed to the device.

— Procedure-related: any AE that results from the implant procedure. Events in this category are directly related to the general procedural sequelae.

— Patient condition-related: any AE that results from the worsening of a pre-existing condition or cannot be attributed to the device or procedure.

— Other: any AE that cannot be assigned to any of the above three causes. It is important that every effort is made, including the use of imaging and other investigations where appropriate, to determine the cause.

In addition to establishing this causal relationship, the probability of relationship shall also be established by categorizing each AE as either definitely, possibly or not related to the device, procedure or patient condition. In the case of thromboembolic events that occur in patients with atrial fibrillation, in which it is usually impossible to ascribe causality with certainty, the event shall be ascribed to the device, as required by the reporting guidelines (see Reference [5]).

An independent, multi-disciplinary committee of qualified experts shall adjudicate causality to assign the specific cause of an adverse event. Formal adjudication of adverse events is intended to manage the ambiguity and bias in assigning causality.

Whenever feasible, post-mortem examination and explant analysis is recommended to capture device related deaths and to ensure proper classification of adverse events. A high percentage of 'unknown cause of death' in any investigation of a new device is of serious concern.

J.8 Classification of adverse events

J.8.1 General

Anticipated adverse events shall be established based on the risk analysis for the specific technology. Risk analysis as defined by ISO 14971 is a systematic approach that uses available information to predict device-related hazards to estimate risk. ISO 14155 requires that the risk analysis shall include or refer to an objective review of published and available unpublished medical and scientific data and that the residual risks, as identified in the risk analysis, as well as risks to the subject associated with the clinical procedure required by the clinical investigation plan (CIP), be balanced against the anticipated benefits to the subjects. Anticipated adverse events identified via the risk analysis shall be clearly specified in the CIP prior to the initiation of the study. Unanticipated adverse events shall be recorded as such and the causality appropriately adjudicated.

NOTE Risk is defined as the combination of the severity of the harm (or adverse event) and the probability of the occurrence of harm.

For the incidence of AEs to be compared between heart valve replacement systems in randomized trials, it is important that the same definitions and methods of data collection are used in both groups. It is also important that composite endpoints which combine clinical safety and effectiveness are avoided, because the individual components of safety and effectiveness may move in opposite directions.

The most recent definitions of specific adverse events shall be used for data collection on events related to the implantation procedure and the peri-procedural period, and AEs shall be reported as a simple percentage for the first 30 d.

For long-term follow-up beyond 30 d, linearized rates (events per 100 patients/years) and Kaplan-Meier actuarial analysis shall be used (see Reference [5]) for reporting adverse events.

Potential adverse events identified by the risk analysis that are not included in the published guidelines should be defined based on relevant/contemporary references.

Examples of adverse events that shall be reported are provided below. This list is not intended to be all-inclusive but representative of adverse events associated with surgical heart valves. Some events may potentially have more than one causality.

J.8.2 Examples of adverse events

a) Events associated with surgical access:

   1) vascular dissection;

   2) complications of cardiopulmonary bypass;

   3) major bleeding;

   4) chest re-opening for postoperative bleeding;

   5) tamponade, including late tamponade;

   6) sternal non-union or sternal dehiscence;

   7) superficial wound infection;

   8) mediastinitis/pericarditis;

   9) local permanent vascular damage leading to stenosis, aneurysm, embolism or limb ischaemia, or requiring surgical repair.

b) Events associated with LV apex access (e.g. LV vent):

   1) apical aneurysm and pseudo-aneurysm;

   2) apical rupture;

   3) apical wall motion abnormality.

c) Events associated with cardiac damage:

   1) cardiac perforation, including unplanned septal perforation, with or without tamponade;

   2) pericardial effusion including effusion complicated by tamponade, including late tamponade;

   3) damage to the structure or function of a non-target valve;

   4) clinically relevant atrial septal defect;

   5) new, other than transient, arrhythmia;

   6) new or worsened conduction disturbance;

7) myocardial infarction;

8) low cardiac output requiring mechanical support.

d) Events associated with implant procedure:

1) coronary ostial obstruction or coronary artery compression;

2) obstruction to transvalvular flow;

3) valve malposition;

4) valve migration or embolization;

5) stroke or other embolism, including coronary embolism, during the procedure or within 24 h;

6) necessity for re-intervention during the initial procedure.

e) Events associated with organ damage:

1) kidney injury;

2) respiratory failure;

3) liver failure;

4) septicaemia;

5) haematological disorders [e.g. disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT)];

6) pulmonary embolism;

7) worsening heart failure.

f) Potential device-related events:

1) haemolysis;

2) infective endocarditis;

3) stroke or other embolism, including coronary embolism, not clearly associated with the valve implantation;

4) major bleeding not clearly associated with surgical access;

5) valve thrombosis (leaflet thrombosis of even only one leaflet should be documented as valve thrombosis);

6) paravalvular leak;

7) pannus;

8) transvalvular regurgitation;

9) stenosis;

10) reintervention to repair, alter, adjust, reposition, dilate, retrieve or replace a previously implanted prosthesis;

11) acute decompensated heart failure;

12) unexplained death (the reporting guidelines (see Reference [5]) require these deaths to be included in device-related mortality).

In the case of surgery-related bleeding, blood loss during cardiopulmonary bypass is impossible to quantify accurately because all intracardiac and intrapericardial blood is returned to the cardiopulmonary bypass circuit. Postoperative blood loss through drainage tubes can be measured but for consistent reporting shall be limited to measured blood loss in the first 24 h, because drains left in place beyond this period often continues to drain a combination of blood and fluid with the fluid component gradually increasing with time, i.e. not true blood loss. An immediate post-operative fall in haemoglobin that occurs in almost all patients and that resolves without transfusion should not be interpreted as blood loss because in most cases it is due to haemodilution consequent upon the addition of clear fluid to prime the cardiopulmonary bypass circuit.

J.9 Follow up of SAEs

Any SAE shall be followed until it has resolved or in the investigator's opinion it is no longer clinically relevant. The long-term outcome shall be reported, including permanent device-related impairment (see Reference [5]).

J.10 Device-related mortality

Consistent with the reporting guidelines (see Reference [5]), all device-related mortality shall be reported. It includes any death caused by structural valve deterioration, non-structural dysfunction (e.g. PVL, pannus, inappropriate sizing or positioning, haemolysis), valve thrombosis, embolism, bleeding event (e.g. related to antithrombotic medication), prosthetic endocarditis, death related to reintervention, or sudden, unexplained death. Deaths caused by heart failure require particularly detailed documentation of investigations performed prior to death in order to distinguish between device-related deaths and deaths due to deteriorating myocardial function unrelated to the device. If the cause of heart failure cannot be determined, the death should be ascribed to the device.

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National Annex A

(*National Foreword*)

A-1 BIS CERTIFICATION MARKING

The product(s) conforming to the requirements of this standard may be certified as per the conformity assessment schemes under the provisions of the *Bureau of Indian Standards Act*, 2016 and the Rules and Regulations framed thereunder, and the product(s) may be marked with the Standard Mark.

(*Continued from second cover*)

The standard also makes a reference to the BIS Certification Marking of the product. Details of which are given in National Annex A.

For the purpose of deciding whether a particular requirement of this standard is complied with the final value, observed or calculated, expressing the result of a test or analysis shall be rounded off in accordance with IS 2 : 1960 ‘Rules for rounding off numerical values (*revised*)’. The number of significant places retained in the rounded off value should be the same as that of the specified value in this standard.

Bureau of Indian Standards

BIS is a statutory institution established under the *Bureau of Indian Standards Act*, 2016 to promote harmonious development of the activities of standardization, marking and quality certification of goods and attending to connected matters in the country.

Review of Indian Standards

Amendments are issued to standards as the need arises on the basis of comments. Standards are also reviewed periodically; a standard along with amendments is reaffirmed when such review indicates that no changes are needed; if the review indicates that changes are needed, it is taken up for revision. Users of Indian Standards should ascertain that they are in possession of the latest amendments or edition by referring to the website- www.bis.gov.in or www.standardsbis.in.

This Indian Standard has been developed from Doc No.: MHD 06 (18159).

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