NORMA
EUROPEA

Impianti cardiovascolari
Protesi valvolari cardiache

UNI EN ISO 5840

SETTEMBRE 2009

Cardiovascular implants
Cardiac valve prostheses

La norma si applica a tutti i dispositivi destinati ad essere impiantati nel cuore umano, come valvole cardiache sostitutive.

1 Scope

1.1 This International Standard is applicable to all devices intended for implantation in human hearts, as a heart valve substitute.

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

1.3 This International Standard outlines an approach for qualifying the design and manufacture of a heart valve substitute through risk management. The selection of appropriate qualification tests and methods are derived from the risk assessment. The tests may include those to assess the physical, chemical, biological and mechanical properties of heart valve substitutes and of their materials and components. The tests may also include those for pre-clinical *in vivo* evaluation and clinical evaluation of the finished heart valve substitute.

1.4 This International Standard imposes design specifications and minimum performance specifications for heart valve substitutes where adequate scientific and/or clinical evidence exists for their justification.

1.5 This International Standard excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.

NOTE A rationale for the provisions of this International Standard is given in Annex A.

3 Terms and definitions

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

3.1
accessories
device-specific tools that are required to assist in the implantation of the heart valve substitute

3.2
actuarial
statistical technique for estimating survival curves prior to the death of the last member of a cohort

NOTE Some examples are the "Kaplan-Meier" technique and the "life-table" technique.

3.3
anticoagulant-related haemorrhage
internal or external bleeding that causes death or stroke, or that requires transfusion, operation or hospitalization

NOTE This definition is restricted to patients who are receiving anticoagulants and/or antiplatelet drugs, and excludes minor bleeding events.

3.4
arterial diastolic pressure
minimum value of the arterial pressure during diastole

3.5
arterial peak systolic pressure
maximum value of the arterial pressure during systole

3.6
back pressure
differential pressure applied across the closed valve

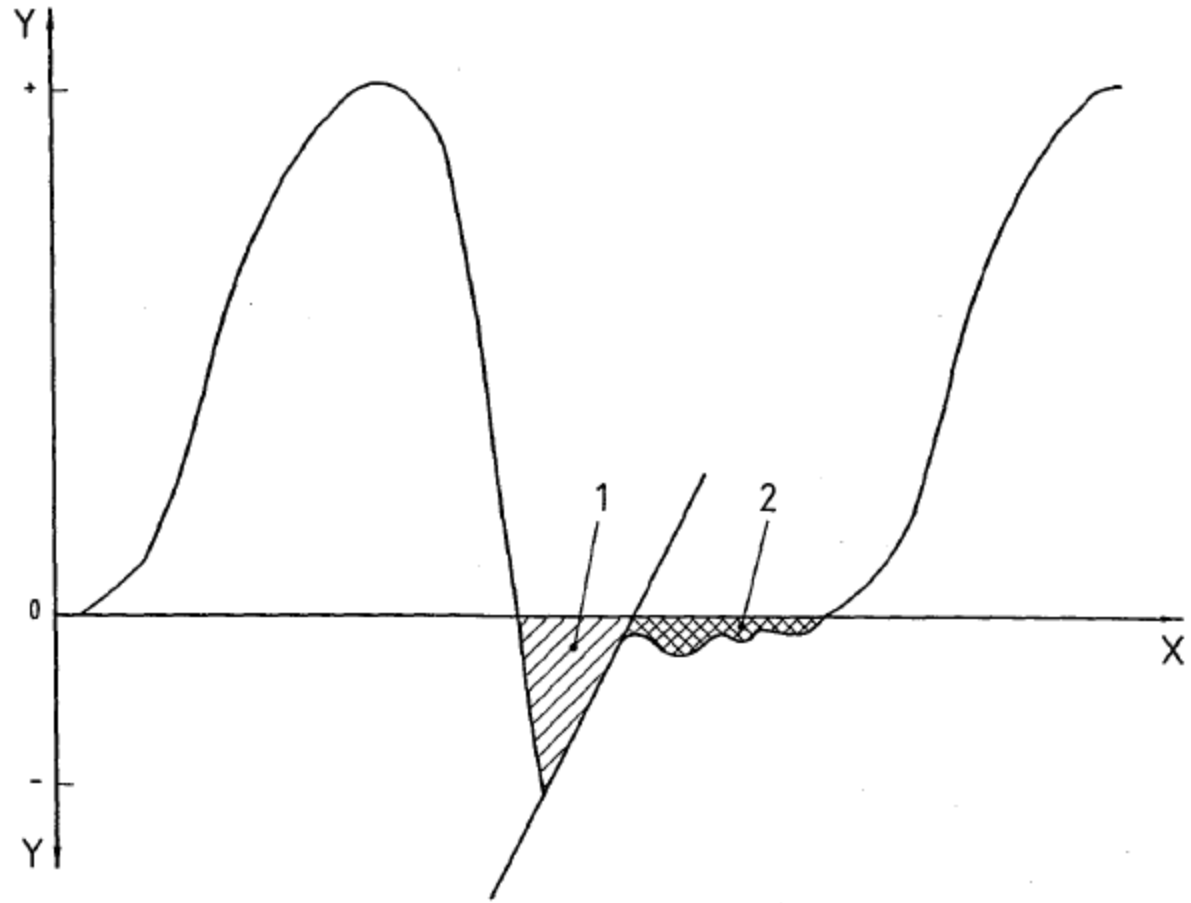
3.7
blood-equivalent fluid
fluid whose physical properties, e.g. specific gravity, viscosity, approximate those of blood

3.8
closing volume
component of the regurgitant volume that is associated with the dynamics of valve closure during a single cycle

See Figure 1.

3.9
control valve
heart valve substitute for preclinical and clinical evaluations of similar design and constructed of similar material as the investigational device

NOTE The control valve should have a known clinical history.



Key

X time
Y flowrate
1 closing volume
2 leakage volume

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

3.10
cumulative incidence
statistical technique where events other than death can be described by the occurrence of the event over time without including death of the subjects

NOTE Cumulative incidence is also known as 'actual' analysis.

3.11
cycle
one complete sequence in the action of a heart valve substitute under pulsatile-flow conditions

3.12
cycle rate
number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)

3.13
design verification
establishment by objective evidence that the design output meets the design input requirements

3.14
design validation
establishment by objective evidence that device specifications conform with user needs and intended use(s)

3.15
effective orifice area
A_{EO}
orifice area that has been derived from flow and pressure or velocity data

3.16
failure
inability of a device to perform its intended function at any point during its intended lifetime

NOTE The inability to perform the intended function may manifest itself as a reduced operating effectiveness and/or as hazards.

3.17
failure mode
mechanism of failure which can result in a hazard

NOTE Stent fracture, calcification and prolapse are examples of failure modes.

3.18
flexible heart valve substitute
heart valve substitute wherein the occluder is flexible under physiological conditions

NOTE The orifice ring may or may not be flexible. This category was previously known as biological heart valve substitute because of the biological source of the flexible occluder(s) but, at a minimum, should also include flexible polymer occluder(s).

3.19
forward-flow phase
portion of the cycle time during which forward flow occurs through a heart valve substitute

3.20
hazard
known or potential source of harm which results from a given failure mode

3.21
harm
physical injury or damage to the health of the patient or end-user of the device

NOTE Adapted from ISO/IEC Guide 51:1999 [14], definition 3.3.

3.22
heart valve substitute
device used to replace or supplement a natural valve of the heart

See also 3.18 and 3.48, and examples in Figures J.1, J.2, J.3, J.4 and J.5.

3.23
intended use
use of a product, process or service in accordance with the specifications, instructions and information provided by the manufacturer

3.24
internal orifice area
IOA
numerical indication of the area within a prosthetic heart valve through which blood flows

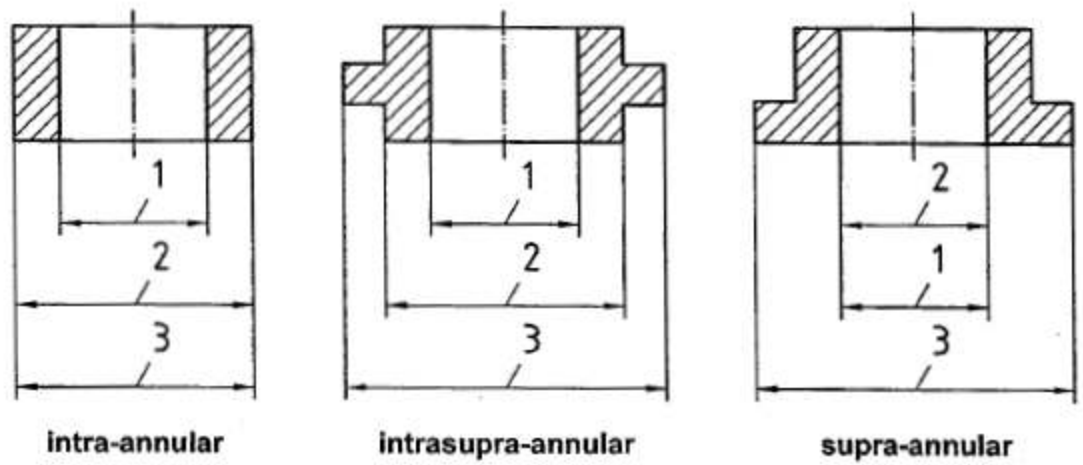
See Figure 2.

3.25
intra-annular sewing ring
sewing ring designed to secure the heart valve wholly or mostly within the patient's tissue annulus

See Figure 2. See also 3.24, 3.66 and 3.70.

3.26
intrasupra-annular sewing ring
sewing ring designed to secure a portion of the valve or sewing ring above the patient's tissue annulus and also some portion of the valve within the patient's tissue annulus

See Figure 2. See also 3.24, 3.66 and 3.70.



Key
1 IOA
2 TAD
3 ESRD

Figure 2 — Designation of dimensions of heart valve substitute sewing ring configurations

3.27
isolated (aortic or mitral) heart valve substitute
implantation of single heart valve substitute excluding patients who have a second heart valve substitute in a different anatomical position

NOTE Concomitant procedures, including valve repair, coronary artery bypass, and ascending aortic aneurysm repair, are not relevant to this definition. See 7.4.4.

3.28
leakage volume
component of the regurgitant volume which is associated with leakage through the closed valve during a single cycle

NOTE The point of separation between the closing and leakage volumes is obtained according to a defined and stated criterion (the linear extrapolation shown in Figure 1 is just an example).

3.29
linearized rate
linearized rate for a complication is the total number of events divided by the total time under evaluation

NOTE Generally, the rate is expressed in terms of percent per patient year.

3.30
long term follow-up
continued (after regulatory approval) periodic assessment of patients who have received the heart valve substitute during the clinical evaluation

3.31
manufacturer
organization with responsibility for the design, manufacture, packaging or labelling of a medical device, assembling a system, or adapting a medical device before it is placed on the market, regardless of whether these operations are carried out by the organization or on their behalf by a third party

3.32
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one cycle

3.33
mean pressure difference
time-averaged arithmetic mean value of the pressure difference across a heart valve substitute during the forward-flow phase of the cycle

NOTE The use of "mean pressure gradient" for this term is deprecated.

3.34
nonstructural dysfunction
abnormality resulting in stenosis or regurgitation of the heart valve substitute that is not intrinsic to the valve itself

NOTE This dysfunction is exclusive of valve thrombosis, systemic embolus or infection diagnosed at re-operation, autopsy or *in vivo* investigation. Examples include entrapment by pannus or suture, paravalvular leak, inappropriate sizing, and significant haemolytic anaemia.

3.35
occluder
component(s) of a heart valve substitute, such as rigid or flexible leaflets, discs, and balls, that move(s) to inhibit backflow

3.36
operative mortality
death from any cause during operation or within 30 d of the operation

3.37
outflow tract profile height
maximum distance that the valve extends axially into the outflow tract in the open or closed position, whichever is greater, measured from the valve structure intended to mate with the top (atrial or aortic side) of the patient's annulus

3.38
pannus
ingrowth of tissue into the heart valve substitute which may interfere with normal functioning

3.39
paravalvular leak
clinically or haemodynamically detectable defect between the heart valve substitute and the patient's annulus

NOTE The term "perivalvular" is deprecated.

3.40
probability
statistical likelihood that a specific event will occur

3.41
process validation
establishing, by objective evidence, that a process consistently produces a result or product that meets its predetermined specifications

3.42
profile height
maximal axial dimension of a heart valve substitute in the open or closed position, whichever is greater

3.43
prosthetic valve endocarditis
infection involving a heart valve substitute

NOTE Diagnosis is based on customary clinical criteria, including an appropriate combination of positive blood cultures, clinical signs (fever, new or altered cardiac murmurs, splenomegaly, systemic embolus or immunopathologic lesions) and/or histologic confirmation of endocarditis at reoperation or autopsy. Morbidity associated with active infection such as valve thrombosis, embolus or paravalvular leak is included under this category and is not included in other categories of morbidity.

3.44
quasi-real time durability testing
long-term durability testing performed at a cycle rate between normal and high normal (up to 200 cycles/min)

3.45
reference valve
heart valve substitute used to assess the conditions established in the *in vitro* tests used to evaluate the test heart valve substitute

3.46
regurgitant fraction
regurgitant volume expressed as a percentage of the stroke volume

3.47
regurgitant volume
volume of fluid that flows through a heart valve substitute in the reverse direction during one cycle and is the sum of the closing volume and the leakage volume

See Figure 1.

3.48
rigid heart valve substitute
heart valve substitute wherein the occluder(s) and orifice ring are non-flexible under physiological conditions

NOTE This category was previously known as mechanical heart valve substitute. Materials of construction of the rigid components of rigid heart valve substitutes have historically been metals, pyrolytic carbon and polymers.

3.49
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999 [14], definition 3.2]

3.50
risk analysis
systematic use of available information to identify hazards and to estimate the associated risks

NOTE Adapted from ISO/IEC Guide 51:1999 [14], definition 3.10.

3.51
risk assessment
overall process comprising a risk analysis and a risk evaluation

[ISO/IEC Guide 51:1999 [14], definition 3.12]

3.52
risk control
process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels

3.53
risk estimation
process used to assign values to the probability and consequences of a risk

3.54
risk evaluation
judgment, on the basis of risk analysis, of whether an acceptable level of risk has been achieved in a given context based on the current values of society

NOTE Adapted from ISO/IEC Guide 51:1999 [14], definitions 3.7 and 3.11.

3.55
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk

3.56
root mean square forward flow
RMS forward flow
square root of the integral of the volume flow waveform squared

NOTE 1 This is calculated using Equation (1).

$$q_{v\,RMS} = \sqrt{\frac{\int_{t_1}^{t_2} q_v(t)^2 dt}{t_2 - t_1}} \qquad (1)$$

where

$q_{v\,RMS}$ is root mean square forward flow;
$q(t)$ is instantaneous flow at time t;
t_1 is time at start of forward flow;
t_2 is time at end of forward flow.

NOTE 2 The rationale for use of $q_{v\,RMS}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate, and it is the mean pressure difference that is required.

3.57
safety
freedom from unacceptable risk

3.58
severity
measure of the possible consequences of a hazard

3.59
simulated cardiac output
net fluid volume forward flow per minute, through a test heart valve substitute

3.60
special processes
those processes for which the product cannot be fully verified by inspection or test

3.61
sterile
free from viable micro-organisms

3.62
sterility assurance level
SAL
probability of a viable micro-organism being present on a product after sterilization

3.63
sterilization
validated process used to render a product free from all forms of viable micro-organisms

3.64
stroke volume
volume of fluid moved through a test heart valve substitute in the forward direction during one cycle

3.65
structural deterioration
change in the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation

3.66
supra-annular sewing ring
sewing ring designed to secure the valve wholly above the patient's tissue annulus

See Figure 2.

3.67
systemic embolism
clot or other particulate matter, not associated with infection, originating on or near the heart valve substitute and transported to another part of the body

NOTE Diagnosis may be indicated by a new, permanent or transient, focal or global neurologic deficit (exclusive of haemorrhage) or by any peripheral arterial embolus unless proved to have resulted from another cause (e.g. atrial myxoma). Patients who do not awaken post-operatively or who awaken with a stroke or myocardial infarction are excluded. Acute myocardial infarction that occurs after operation is arbitrarily defined as an embolic event in patients with known normal coronary arteries or who are less than 40 y of age.

3.68
tissue annulus diameter
TAD
diameter in millimetres of the smallest flow area within the patient's valve annulus

3.69
validation
confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled

3.70
valve size
manufacturer's designation of a heart valve substitute which indicates the tissue annulus diameter (TAD in millimetres) of the patient into whom the heart valve substitute is intended to be implanted (i.e., TAD = designated valve size)

NOTE This takes into consideration the manufacturer's recommended implant position relative to the annulus and the suture technique. See also A.7, Q.2.2 c), Q.2.3 b) and Q.2.3 g).

3.71
valve thrombosis
blood clot, not associated with infection, causing dysfunction of the heart valve substitute

NOTE Diagnosis may be proved by operation, autopsy or clinical investigation (e.g. echocardiography, angiocardiography or magnetic resonance imaging).

3.72
verification
confirmation by examination and provision of objective evidence that specified requirements have been fulfilled

Table 1 — Heart valve substitute operational environment

Parameter	Description			
Surrounding medium:	Human heart/Human blood			
Temperature:	34 °C to 42 °C			
Heart rate:	30 beats/min to 200 beats/min			
Cardiac output:	3 l/min to 15 l/min			
Stroke volume:	25 ml to 100 ml			
Blood pressures and resultant pressure loads by patient condition:	Arterial peak systolic pressure mm Hg	Arterial diastolic pressure mm Hg	Differential pressure across closed valve	
			Aortic Δp_A mm Hg	Mitral Δp_M mm Hg
Normotensive	100 to 130	65 to 85	95	115
Hypotensive	60	40	50	60
Hypertensive				
Stage 1 (mild)	140 to 159	90 to 99	123	150
Stage 2 (moderate)	160 to 179	100 to 109	138	170
Stage 3 (severe)	180 to 209	110-119	155	195
Stage 4 (very severe)	> 210	> 120	185	210
Extreme (expected maximum pressure for a single cycle)	300	160	230	300

6.2.2 Performance specifications

6.2.2.1 The manufacturer shall establish (i.e. define, document and implement) the clinical performance requirements of the device and the corresponding device performance specifications. The limits for device performance specifications shall be determined by the manufacturer for the specific heart valve substitute design in light of the intended use and claims to be made for the device. The following list of desired clinical and device-based performance characteristics describe a safe and effective heart valve substitute.

6.2.2.2 Specifications shall be defined in respect of at least the following performance characteristics:

— allows forward flow with acceptably small mean pressure difference;

— prevents retrograde flow with acceptably small regurgitation;

— resists embolization;

— resists haemolysis;

— resists thrombus formation;

— is biocompatible;

— is compatible with *in vivo* diagnostic techniques;

— is deliverable and implantable in the target population;

— remains fixed once placed;

— has an acceptable noise level;

— has reproducible function;

— maintains its functionality for a reasonable lifetime, consistent with its generic class;

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

7.2 *In vitro* assessment

7.2.1 Test conditions, sample selection and reporting requirements

7.2.1.1 Test conditions and sample selection

7.2.1.1.1 Test specimens shall emulate, as closely as possible, the condition of the finished product as supplied for clinical use, including exposure to the maximum number of recommended sterilization cycles, where appropriate.

7.2.1.1.2 Where emulation of *in vivo* conditions is applicable to the test method, consideration shall be given to those operational specifications given in Table 1 (see 6.2.1). Where applicable, testing shall be performed using a test fluid of isotonic saline, blood, or a blood-equivalent fluid whose physical properties (e.g. specific gravity, viscosity at working temperatures) are appropriate to the test being performed.

7.2.1.1.3 The choice of test fluid will depend on the test goals and methods, as well as on the valve class. The risk assessment shall play a role in the choice of the test fluid.

7.2.1.2 Reporting requirements

Each test report shall include:

a) the rationale for the test;

b) identification and description of the sample tested (e.g. batch number);

c) identification and description of the reference valve(s);

d) number of specimens tested, and sample size rationale;

e) detailed description of the test method;

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

g) test results and conclusions.

Statistical procedures, such as the ones described in Annex E, may be used to assist data analysis.

7.2.3 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid mechanical performance of the heart valve substitute and provide indicators of valve performance in terms of load to the heart and potential for blood stasis and damage.

A guideline for the performing and reporting of hydrodynamic tests is given in Annex L. The detailed protocols shall be based on the findings of the risk assessment.

Tests shall be carried out on at least three heart valve substitutes of each size and on at least one reference valve of each of the small, medium and large sizes. A different sample size or size distribution may be used if it can be shown from the risk analysis that it provides sufficient information.

The *in vitro* test results shall meet or exceed the minimum performance requirements provided in Table 2, which are given as a function of valve size, TAD, and position. The minimum performance requirements correspond to the following pulsatile-flow conditions: beat rate = 70 cycles/min, simulated cardiac output = 5,0 l/min, mean aortic pressure = 100 mm Hg, and systolic duration = 35 %. The minimum performance requirements are based on values in the published scientific literature.

Table 2 — Minimum performance requirements

Position	Aortic							Mitral			
Valve size (TAD, mm)	19	21	23	25	27	29	31	25	27	29	31
A_{EO} (cm^2)	⩾ 0,70	⩾ 0,85	⩾ 1,00	⩾ 1,20	⩾ 1,40	⩾ 1,60	⩾ 1,80	⩾ 1,20	⩾ 1,40	⩾ 1,60	⩾ 1,80
Regurgitant Fraction (%)	⩽ 10	⩽ 10	⩽ 10	⩽ 15	⩽ 15	⩽ 20	⩽ 20	⩽ 15	⩽ 15	⩽ 20	⩽ 20
NOTE See Yoganathan and Travis [26] and Marquez et al. [16].											

$$A_{EO} = \frac{q_{v\,RMS}}{51{,}6 \times \sqrt{\frac{\Delta p}{\rho}}}$$

where

A_{EO} is the effective orifice area in square centimetres;

$q_{v\,RMS}$ is the root mean square forward flow in millilitres per second;

Δp is the mean pressure difference (measured over the positive pressure period of the forward flow phase) in millimetres of mercury;

ρ is the density of the test fluid in grams per cubic centimetre.

NOTE This equation is derived from the Bernoulli Equation. The constant (51,6) is not dimensionless, thus this equation is only valid with the units shown.

7.2.4.3 Component fatigue assessment

An assessment of the fatigue performance of the heart valve substitute structural components shall be conducted. The lifetime of each structural component shall be determined as the minimum duration for which the component can withstand anticipated repeated loadings associated with *in vivo* conditions.

The manufacturer shall determine and justify the fatigue assessment approach and associated characterization technique adopted in order to best determine the structural lifetime for the specific material and valve/component design.

Suggested guidelines are provided in Annex O.

7.3 Preclinical *in vivo* evaluation

7.3.1 Overall requirements

An appropriate preclinical *in vivo* test programme shall be formulated in order to address relevant valve characteristics specific to the test heart valve substitute.

The preclinical *in vivo* evaluation shall:

a) reflect the haemodynamic performance of the heart valve substitute as assessed *in vitro*;

b) provide an assessment of the surgical handling characteristics of the test heart valve substitute and its accessories;

c) provide data to assess the biological reaction to the heart valve substitute. Consideration should be given but not limited to the following items, as relevant to the specific heart valve substitute under evaluation:

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

   2) haemolysis;

   3) thrombus formation;

   4) embolization;

   5) foreign body reaction (inflammation, rejection);

   6) calcification (flexible valves);

   7) acoustic characteristics (rigid valves), if manufacturer claims are made on this issue;

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

   9) cavitation;

d) use a test heart valve substitute of clinical quality;

e) investigate test heart valve substitute in all positions for which it is intended (aortic, mitral, etc.);

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

g) use the same surgical techniques for the implantation of both the test and the control 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.

7.4 Clinical investigation

7.4.1 Principle

Data are obtained on the safety and performance of a heart valve substitute under normal conditions of use in humans; the side effects and related risks of heart valve substitute implantation are documented. The clinical investigation shall include pre-operative, peri-operative and follow-up data from a specified number of patients, each with a minimum of one-year follow-up, to provide statistical justification for the market release of the heart valve substitute.

7.4.2 General

For new heart valve designs, a clinical investigation shall be carried out in accordance with this International Standard. For modification of an existing valve, a clinical investigation shall be considered, based on the results of a risk analysis that evaluates the modification. The clinical investigation shall be conducted in accordance with ISO 14155-1.

7.4.3 Number of institutions

The clinical investigation shall be conducted in a minimum of 8 institutions. The study shall be designed such that the anticipated minimum number of heart valves implanted at any institution shall be 15 of each type (e.g. aortic or mitral) being evaluated.

7.4.4 Number of patients

A minimum number of 150 recipients of isolated aortic heart valve substitutes and a minimum number of 150 recipients of isolated mitral heart valve substitutes shall be evaluated. If the heart valve substitute is intended for implantation in only one position, a minimum of 150 heart valve substitutes shall be evaluated in that position. There shall be a minimum of 15 implants of each valve size of each valve type (e.g. aortic or mitral). Exceptions are: 8 implants of aortic size 19 or smaller; 8 implants of aortic size 29 or larger; 8 implants of mitral size 23 or smaller; 8 implants of mitral size 33 or larger.