INTERNATIONAL STANDARD

ISO 22679

First edition
2021-11

Cardiovascular implants — Transcatheter cardiac occluders

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Reference number
ISO 22679:2021(E)

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

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Foreword

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

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

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

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

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

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Introduction

The field of transcatheter cardiac occluders has advanced and expanded significantly in recent years. Therefore, a group of engineers, scientists, and clinicians, experts well aware of the problems associated with transcatheter cardiac occluder devices and their development, has prepared this document. This document deals with those areas that will help ensure adequate mitigation of device-associated risks for patients and other users of the device, facilitate quality assurance, and help ensure that the device will be provided in a convenient and usable form. This document emphasizes the need to specify and report types of in vitro testing, preclinical in vivo, and clinical evaluations. It describes the requirements for labels and packaging of the device. The in vitro, preclinical in vivo, and clinical evaluations described in this document are intended to help establish safety and performance of a transcatheter cardiac occluder.

This document outlines an approach for minimizing adverse events from the implantation of a transcatheter cardiac occluder through risk management. The selection of appropriate verification or validation tests and methods are derived from the risk assessment and design input requirements. The tests include those to assess the physical, mechanical, chemical, and biological properties of transcatheter cardiac occluders and of their materials and components. The tests also include those for preclinical in vivo evaluation and clinical evaluation of the transcatheter cardiac occluders.

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Cardiovascular implants — Transcatheter cardiac occluders

1 Scope

This document specifies important in vitro tests including functional and durability characteristics of transcatheter cardiac occluders, and their delivery systems and accessories. This document does not specify exact test methods for functional and durability testing, but it offers requirements and recommendations for performance tests of the cardiac occluder system.

Surgical occluders have been omitted from the scope of this document given their significant differences in device geometry, materials, implantation methods, and test methods as compared to transcatheter cardiac occluders.

This document is applicable to all intracardiac occluders intended for transcatheter implantation in humans (e.g. atrial septal occluder, ventricular septal occluder, patent foramen ovale occluder, left atrial appendage occluder, and paravalvular leak occluders). This document does not cover non-cardiac occluders, but elements of this document can be applicable to patent ductus arteriosus occluders.

The following devices and components are outside the scope of this document: surgical devices, cardiac shunt devices, atrial flow regulators, active components (such as sensors), or degradable or animal tissue components.

This document is applicable to both newly developed and modified cardiac occluders, their accessory devices, packaging, and labelling.

This document defines operational conditions and performance requirements for cardiac occluders where either adequate scientific or clinical evidence, or both, exists for their justification.

NOTE At the time of this document, it is impossible to take all future and emerging technologies into consideration. The cardiac occluder systems based on these new technologies can benefit from evaluation based on the basic requirements of this document. Testing beyond the scope of this document can also be necessary in order to verify and validate these cardiac occluder systems.

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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 10555-1, *Intravascular catheters — Sterile and single-use catheters — Part 1: General requirements*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

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

ISO 11070, *Sterile single-use intravascular introducers, dilators and guidewires*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

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ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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

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

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

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

ISO 15223-1, *Medical devices — Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirements*

ISO 15223-2, *Medical devices — Symbols to be used with medical device labels, labelling, and information to be supplied — Part 2: Symbol development, selection and validation*

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

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO/TS 17665-2, *Sterilization of health care products — Moist heat — Part 2: Guidance on the application of ISO 17665-1*

ISO/TS 17665-3, *Sterilization of health care products — Moist heat — Part 3: Guidance on the designation of a medical device to a product family and processing category for steam sterilization*

ISO 20417, *Medical devices — Information to be supplied by the manufacturer*

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

IEC 62366-1, *Medical devices — Part 1: Application of usability engineering to medical devices*

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

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

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

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

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

3 Terms and definitions

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

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

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

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

3.1
access system
system consisting of a variety of components (e.g. sheath, haemostasis control valve, side ports for administration of physiological fluids and medications) to provide vascular access for the *cardiac occluder* (3.3) *delivery system* (3.8)

3.2
adverse event
AE
untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings), in subjects, users or other persons, whether or not related to the investigational medical device

Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.

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

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

3.3
cardiac occluder
non-active (3.20) implant to occlude a specific cardiac anatomic structure (e.g. atrial septal defects, ventricular septal defects, patent foramen ovale, left atrial appendage) or seal an abnormal site of blood flow (e.g. heart valve substitute paravalvular leak)

3.3.1
atrial septal occluder
cardiac occluder (3.3) used to treat an atrial septal defect

3.3.2
left atrial appendage occluder
cardiac occluder (3.3) used to close the opening of the left atrial appendage

3.3.3
paravalvular leak occluder
cardiac occluder (3.3) used to close a paravalvular leak

3.3.4
patent ductus arteriosus occluder
occluder used to close a patent ductus arteriosus

3.3.5
patent foramen ovale occluder
cardiac occluder (3.3) used to close a patent foramen ovale

3.3.6
ventricular septal occluder
cardiac occluder (3.3) used to treat a ventricular septal defect

3.4
cardiac occluder system
supplied components, such as the *cardiac occluder* (3.3), *access system* (3.1), *delivery system* (3.8), accessories, packaging and labelling

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3.5
delivery approach
anatomical access used to deliver the *cardiac occluder* (3.3) to the intended *implant site* (3.17) (e.g. transfemoral, transseptal)

3.6
delivery catheter
component of the *delivery system* (3.8), used to advance and deploy a *cardiac occluder* (3.3) to the intended implantation site

3.7
delivery sheath
hollow tube that traverses the skin and subcutaneous tissue and enters the endovascular space to facilitate entry of wires and catheters

3.8
delivery system
system [e.g. *delivery catheter* (3.6)] used to deliver, deploy, attach or adjust [i.e. *recapture* (3.22) or retrieve] a *cardiac occluder* (3.3) in the intended implantation site

3.9
design validation
establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.18)

3.10
design verification
establishment by objective evidence that the design output meets the design input requirements

3.11
device embolization
post-deployment or peri-procedural dislodgement of the *cardiac occluder* (3.3), from the implantation site or catheter, respectively, to an unintended and non-therapeutic location via the bloodstream

3.12
device failure
inability of a *cardiac occluder* (3.3) to perform its intended function sufficient to cause a hazard

3.13
device migration
detectable movement or displacement of the *cardiac occluder* (3.3) from its original position within close proximity of the intended *implant site* (3.17), without embolization

3.14
failure mode
mechanism of *device failure* (3.12) [e.g. catastrophic support structure *fracture* (3.15)]

3.15
fracture
unintentional disruption, under the action of applied load (e.g. force, torque, or deformation), of a *structural element* (3.32) of the *cardiac occluder system* (3.4) that were previously intact

3.16
imaging modality
imaging method used to facilitate diagnosis, delivery and/or *retrieval* (3.24)/*recapture* (3.22) of the implant within the target *implant site* (3.17), as well as to assess *cardiac occluder* (3.3) performance after implantation

3.17
implant site
intended anatomic site of a *cardiac occluder* (3.3) deployment

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3.18
intended use
use of a *cardiac occluder* (3.3) in accordance with the specifications, instructions and information provided by the manufacturer

3.19
membrane
flexible synthetic material covering or integrated within a portion or all of the cardiac occlude

3.20
non-active
implant which does not depend on a source of electrical energy or any source of power other than that directly generated by the human body or gravity

3.21
protective packaging
configuration of materials designed to prevent damage to the *sterile barrier system* (3.31) and its contents from the time of their assembly until the point of use

[SOURCE: ISO 11607-1:2019, 3.14]

3.22
recapture
process of returning the *cardiac occluder* (3.3) back into the *delivery system* (3.8), following partial or full deployment, but prior to its release

3.23
repositioning
change in implant position and/or orientation of a partially or fully deployed *cardiac occluder* (3.3) via a transcatheter technique, possibly requiring full or partial recapturing of the device

3.24
retrieval
removal of a partially or fully deployed *cardiac occluder* (3.3) via a transcatheter or surgical technique

3.25
risk
combination of the probability of occurrence of harm and the *severity* (3.30) of that harm

[SOURCE: ISO 14971:2019, 3.18]

3.26
risk analysis
systematic use of available information to identify hazards and to estimate the associated *risk(s)* (3.25)

[SOURCE: ISO 14971:2019, 3.19, modified — "associated" has been added and "(s)" has been added to "risk".]

3.27
risk assessment
overall process comprising a *risk analysis* (3.26) and a *risk* (3.25) evaluation

[SOURCE: ISO 14971:2019, 3.20]

3.28
sample size
quantity of individual specimens of a device tested

[SOURCE: ASTM F3172-15:2015, 3.1.13]

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3.29
safety
freedom from unacceptable *risk* (3.25)

[SOURCE: ISO 14971:2019, 3.26]

3.30
severity
measure of the possible consequences of a hazard

[SOURCE: ISO 14971:2019, 3.27]

3.31
sterile barrier system
minimum package that minimizes the *risk* (3.25) of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11607-1:2019, 3.23]

3.32
structural element
stent or frame component of a *cardiac occluder* (3.3)

3.33
withdrawal
removal of the occluder *delivery system* (3.8) with or without the *cardiac occluder* (3.3)

4 Abbreviations

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

ADE	adverse device effect
AE	adverse event
AFib	atrial fibrillation
ASD	atrial septic defect
CEC	Clinical Events Committee
CIP	clinical investigation plan
CMR	cardiac magnetic resonance
CRF	case report form
CT	computed tomography
DIC	disseminated intravascular coagulation
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
GCP	Good Clinical Practice
HIT	heparin-induced thrombocytopenia
ICE	intracardiac echocardiography

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IFU	instructions for use
IRB	Institutional Review Board
LAA	left atrial appendage
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PMCF	post-market clinical follow-up
PDA	patent ductus arteriosus
PET	position emission tomography
PFO	patent foramen ovale
PVL	paravalvular leak
SADE	serious adverse device effect
SAE	serious adverse event
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
VSD	ventricular septal defect

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5 Fundamental requirements

5.1 General

The activities described within this document shall be carried out within a formal quality system.

NOTE ISO 13485 contains requirements for a suitable quality system for a medical manufacturer. Additional requirements can be specified by a country or region.

5.2 Risk management

The manufacturer shall define, implement and document risk management activities in accordance with ISO 14971. A risk-based methodology challenges the manufacturer to continually analyse and evaluate known and theoretical risks of the device, to develop the most appropriate methods for mitigating the risks of the device, and to implement the appropriate test, analysis methods, or rationale to demonstrate the residual risks are acceptable (see Annex A).

Annex B provides an example of a hazard analysis to serve as a starting point for a risk analysis specific to some cardiac occluder devices.

Annex I provides definitions and examples of adverse events that can be useful in the risk management process.

As part of the risk management process, the manufacturer shall establish, document, implement and maintain a usability engineering process, linked but distinct from the device design process, as detailed in IEC 62366-1.

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6 Device description

6.1 General

The requirements of ISO 14630 shall apply.

6.2 Intended use

The manufacturer shall identify the pathological condition(s) to be treated, the intended patient population and intended claims. The manufacturer shall also consider the intended user(s) of the medical device and the environments in which it is used.

6.3 Design inputs

6.3.1 Operational principles and specifications

The manufacturer shall define the operational specifications for the device including the principles of operation, intended device delivery approach or process, durability, shelf life, shipping or storage limits, and the physiological environment in which it is intended to function. The manufacturer shall define relevant anatomical characteristics and device dimensional parameters that will be required to select either the device model or size, or both. Additionally, if designed for periprocedural modification, define how the device configuration will be determined (see Annex O and Annex G).

6.3.2 Functional, performance and safety requirements

6.3.2.1 General

The manufacturer shall establish (i.e. define, document and implement) the functional, performance and safety requirements of the cardiac occluder system for the intended use and device claims.

6.3.2.2 Implantable device

The intended performance of the cardiac occluder device shall take into consideration at least the following:

a) the ability to occlude undesired blood flow;

b) the ability to resist migration and embolization;

c) the ability to minimize haemolysis;

d) the ability to minimize undesired thrombus formation;

e) biocompatibility;

f) the ability to resist corrosion;

g) the ability to minimize particulate shedding;

h) compatibility with adjacent anatomical structures or other implanted devices, if applicable;

i) compatibility with diagnostic imaging techniques (e.g. MRI);

j) visibility under diagnostic imaging techniques (e.g. MRI, echocardiography, fluoroscopy, CT);

k) deliverability and implantability in the target population;

l) the ability to maintain structural and functional integrity during the expected lifetime of the device;

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m) the ability to maintain structural integrity, functionality and sterility for the labelled shelf life prior to implantation;

n) the ability to be consistently and safely prepared for implantation;

o) the ability to be consistently and safely implanted in the intended implantation site and achieve the aforementioned performance objectives;

p) the ability to be either safely retrieved, adjusted or repositioned, or all, if applicable.

NOTE See ISO 14630.

6.3.2.3 Access and delivery system

The functional, performance and safety requirements of the access and delivery system shall be established (see Annex M). All supplied sterile single-use intravascular catheters shall follow ISO 10555-1. If sterile single-use intravascular introducers, dilators or guidewires are supplied by the manufacturer, then they shall follow ISO 11070, as applicable. For cardiac occluder systems which either require or allow the user to select a non-supplied access system, the attributes of the non-supplied access system shall be established for it to be compatible with the cardiac occluder delivery system. These attributes include minimum inner diameter and length.

The design attributes shall take into consideration at least the following to meet the intended performance of the delivery and access system:

a) compatibility of the access system, delivery system, and the cardiac occluder;

b) the ability to permit consistent, accurate and safe loading, access, delivery, deployment and release of the cardiac occluder to the intended implantation site;

c) the ability to permit consistent and safe withdrawal of the delivery system prior to and after deployment of the cardiac occluder device;

d) the ability to minimize thrombus formation;

e) the ability to minimize blood loss;

f) the ability to either retrieve, reposition, or remove the cardiac occluder device, or all, if applicable;

g) biocompatibility;

h) the ability to resist corrosion;

i) the ability to maintain integrity of the coating, if applicable;

j) the ability to minimize particulate generation;

k) the ability to maintain its functionality and sterility for the labelled shelf life;

l) compatibility and visibility with diagnostic imaging techniques (e.g. MRI, echo, fluoroscopy, CT), if applicable;

m) compatibility with tools and accessories required to complete the procedure.

n) the ability to avoid air thrombus during the procedure;

o) the ability to inject contrast agent through the applicable changes of the procedure, if applicable.

6.3.3 Implant procedure: Device and usability requirements

The cardiac occluder system shall provide intended users the ability to safely and effectively perform pre-operative, intra-operative, and post-operative procedural tasks to achieve desired outcome. This shall include procedure-specific tools and accessories that intended users will need to complete the

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procedure. In addition to establishing the device physical requirements during the implant procedure, the usability engineering process according to IEC 62366-1 shall be used to establish user interface characteristics that can be related to safety and effectiveness during the implant procedure.

6.3.4 Packaging, labelling and sterilization

The cardiac occluder system shall meet the requirements for packaging, labelling, and sterilization contained within Annex C, Annex D, and Annex E, respectively.

The manufacturer shall provide information and guidance (e.g. imaging modalities and sizing procedure) in the labelling to allow for appropriate preparation of the implantation site (e.g. left atrial appendage), selection of appropriate implant size, implantation of the cardiac occluder, and post-procedure care and medication, if applicable. The manufacturer shall also provide MRI safety information in the labelling.

See ISO 11135, ISO 11137-1, ISO 11137-2, ISO 11137-3, ISO 14160, ISO 14937, ISO 17665-1, ISO/TS 17665-2, and ISO/TS 17665-3 for additional information regarding sterilization.

See ISO 11607-1 and ISO 11607-2 for additional information regarding packaging.

See ISO 15223-1, ISO 15223-2, and ASTM F2503 for additional information regarding labelling,

6.4 Design outputs

Design and development outputs shall meet the requirements of ISO 13485.

The manufacturer shall establish (i.e. define, document and implement) a specification of the cardiac occluder system. In addition to the physical components of the cardiac occluder system, the manufacturer shall establish instructions and specifications for the implant procedure. Instructions shall meet the requirements of Annex D.

6.5 Design transfer (manufacturing verification or validation)

Design transfer requirements shall meet the requirements of ISO 13485.

The manufacturer shall establish (i.e. define, document and implement) the manufacturing process operations and inspection steps including components and manufacturing materials.

As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the process is capable of consistently delivering quality product. The risk management file shall identify and justify the verification or validation activities necessary to demonstrate the acceptability of the process settings chosen.

The manufacturer shall establish the adequacy of full-scale manufacturing by validation of the manufacturing process (the installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)).

7 Design verification and validation

7.1 General requirements

The manufacturer shall perform design verification to demonstrate that the design output of a cardiac occluder system meets the design input. The manufacturer shall establish a design verification strategy relating to hazards identified from the risk analysis. The protocols shall identify the test purpose, setup, equipment (e.g. specifications, calibration), test conditions (with a justification of appropriateness to anticipated in vivo operating conditions for the device, if applicable), acceptance criteria, and sample quantities to be tested. Design verification includes testing, analyses, and other activities.

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The manufacturer shall also validate the design of the cardiac occluder system to ensure that the device meets user needs and intended use; refer to applicable sections of ISO 13485. The design verification and validation shall address all risks identified in the risk assessment at the appropriate level.

NOTE See ISO/IEC 17025[50] regarding considerations for test method validation.

7.2 In vitro assessment

7.2.1 General

In vitro assessment shall be used, where appropriate, to demonstrate mitigation of risks identified in the risk analysis through either design verification or validation, or both.

7.2.2 Test conditions, sample selection and reporting requirements

7.2.2.1 Test conditions

The test conditions for each in vitro assessment shall be defined and justified (see Annex G and Annex O for examples of differential pressures).

7.2.2.2 Test sample selection

Test samples for either design verification or validation, or both, shall represent the cardiac occluder system product intended for clinical use. Representative products include initial production units, batches or their equivalents. Test samples shall be appropriately preconditioned prior to testing, including exposure to the maximum number of allowed sterilization cycles, process chemicals, aging effects, shipping/handling, in accordance with all manufacturing procedures and instructions for use, where appropriate. Any deviations of the test samples from the finished product shall be justified.

The full range of available device configurations (e.g. sizes, deployment shapes, use ranges, delivery system and accessories, and implant sites) shall be considered during selection of test samples; however, depending on the particular test, testing does not necessarily have to be completed for each device configuration.

For all tests, the number of samples shall be justified based on the specific intent of the test, with a scientific justification. Additional information regarding sampling and sample conditioning, including any loading and deployment steps (including repositioning and recapturing, if applicable) in accordance with the instructions for use, where appropriate shall be included within each test method defined herein, as appropriate. Samples shall be subjected to conditions that are normally encountered that affect the test results. Examples of conditioning are preparation of the occluder system, loading the occluder inside the delivery catheter, passage through simulated tortuous vasculature, warming of the system to body temperature and deployment of the occluder. If retrieval and repositioning is indicated for the implant in the IFU, the maximum allowable number of re-sheathing/recapturing and deployment cycle(s) specified shall be simulated in clinically representative challenging conditions.

NOTE See ASTM F3172[18].

7.2.2.3 Reporting requirements

The test report or accompanying documentation from the manufacturer shall include:

a) the purpose, scope and rationale for the test;

b) identification, description and rationale for the selection of the cardiac occluder system elements tested (e.g. lot number, size, configuration) and prior history [e.g. packaging, sterilization, ageing (accelerated, real-time), simulated use (tracking, positioning, deployment)];

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

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

e) description of the test method with reference to detailed test method;

f) the pre-specified acceptance criteria shall be provided, or justified if excluded;

g) either a justification or the clinical relevance of the acceptance criteria, or both shall be provided or referenced, if applicable;

h) verification that appropriate quality assurance standards have been met (e.g. ISO/IEC 17025[50]);

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

j) test results;

k) conclusions (i.e. specify whether the acceptance criteria were met or not, and interpretation of the results).

Statistical procedures used in data analysis and rationale for their use shall be described. Test results and the conclusions shall be used as an input to the risk management documentation to assess the risk associated with a hazard/failure mode under evaluation.

7.2.3 Material property assessment

7.2.3.1 General

The material selection and other requirements of ISO 14630 shall apply.

When functional testing of the device addresses the known potential risks associated with its materials, no specific material properties testing is needed. However, if risks associated with specific material properties are not evaluated within the functional tests conducted for other sections in 7.2 (see Annexes H, J, L and M for example tests), then specific testing of the material properties shall be conducted to address the associated risk.

Material properties used as inputs in computational, structural, durability or other performance assessments, shall be measured and reported as appropriate to risk management.

Material properties deemed to require evaluation outside of functional testing shall be measured on components of the finished system or specimens manufactured and processed the same as the corresponding component(s) of the finished system.

Scientific literature citations or previous characterization data from similar devices may be referenced; however, the applicability of the literature and characterization data to the cardiac occluder shall be justified.

NOTE Material properties reported in literature or from manufacturer's previous studies rather than those measured directly can be used for computational models where the results of the model are sufficiently insensitive to the material properties in the range of the reported ranges of the material properties or if the context of use of the model does not require a high level of predictive confidence (see Reference [9]).

7.2.3.2 Biological safety

The biocompatibility of the materials and components used in the cardiac occluder system shall be assessed in accordance with ISO 10993-1. The test plan recorded in the risk management file shall comprise a biological safety evaluation programme with a justification for the appropriateness and adequacy of the information obtained. The documentation shall include a rationale for the commission of any biological safety tests carried out to supplement information obtained from other sources and for the omission of any tests identified by ISO 10993-1 but not performed. During the hazard identification stage of a biological safety evaluation, information shall be obtained to allow the identification of toxicological hazards and the potential for effects on relevant haematological characteristics.

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Where an identified hazard has the potential for significant clinical effects, the toxicological risk shall be characterized through established methods (e.g. dose-response, exposure level, biochemical interactions, and toxicokinetics in relation to a patient population, and mode of action).

If components contain materials of animal origin, associated risks shall be assessed in accordance with ISO 22442-1.

7.2.4 Structural performance assessment

7.2.4.1 General

An assessment of the ability of the implant to withstand the loads to which it will be subjected shall be performed in order to evaluate the risks associated with potential structural failure modes.

7.2.4.2 Fatigue and durability — In vitro testing

The manufacturer shall assess the durability of the cardiac occluder under simulated in vivo loading conditions. Durability assessment addresses the integrity of the entire cardiac occluder or subassemblies, under extended cyclic loading. Assessment of structural components shall be conducted as part of the fatigue assessment (see Annex H). If appropriate, for the specific device design, the manufacturer shall justify situations where a single test may address both component fatigue and device durability.

An assessment of the durability of the implant shall be performed in order to assess continued function over a reasonable lifetime, considering the intended patient population. Implant durability assessments are typically performed through accelerated testing. Durability testing shall be performed for a minimum of 400 million cycles unless otherwise justified. Testing shall be conducted at clinically relevant challenging conditions. If the labelling for a particular device includes an explicit statement about anticipated in vivo device lifetime, testing shall be performed to support the labelling claim.

Regular inspections (e.g. 50 million, 100 million, 200 million) shall be conducted to assess the consistent loading of the implant. A detailed description of the appearance of the cardiac occluders shall be documented prior to and at the completion of the test. The durability assessment shall be performed by characterization of the test occluder in terms of the observed damage and the extent of damage. The failure modes to be considered and the pass/fail criteria for the test shall be determined based upon the risk assessment. Guidelines for durability testing are provided in Annex H.

Consideration shall be given to variation in deployed occluder shape, which may vary depending on intended cardiac location. In addition, test apparatus shall simulate loading and deformation of the cardiac occluder under in vivo conditions. If an occluder is intended to be implanted in multiple cardiac locations, each location and each failure mode shall be considered in determining the worst-case condition.

The implant shall be loaded (if applicable) and deployed in accordance with the applicable steps of the IFU, and appropriately placed into the test apparatus to simulate the device placement at the intended location.

NOTE See ASTM F1801[12] and ASTM F3211[19].

An assessment of the fatigue performance of the cardiac occluder structural components shall be conducted; all components comprising the support structure, including anchoring features, shall be appropriately considered. Testing shall be performed to demonstrate that the support structure will remain functional for a minimum of 400 million cycles, unless otherwise justified. Acceptance criteria for fatigue testing shall be justified by the manufacturer based on the results of the risk assessment.

The manufacturer shall identify and justify the appropriate in vivo loading and environmental conditions used. If endothelialisation or tissue incorporation of the implant is considered in the interpretation of the test result, scientific justification (e.g. clinical evidence) shall be provided.

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Suggested fatigue assessment guidelines are provided in Annex H.

NOTE See ASTM F1801[12] and ASTM F3211[19], and ASME V&V 40[9].

7.2.4.3 Computational modelling study

In order to predict locations of highest risk of fracture and to mitigate those risks, perform validated computational analyses (e.g. finite element analysis [FEA]) of the structural components of the implant under clinically relevant challenging conditions. Consideration shall be given to critical aspects of the target implant site (e.g. compliance, geometry) and loading from all occluder components. If any symmetry conditions in the computational analyses are utilized, they shall be justified. A validated constitutive model shall be used for each material in the computational model, capturing either time-dependent, temperature-dependent, stress dependent or non-linear material behaviour, or all, as appropriate.

Computational analyses may also be used to establish appropriate test conditions and to select test samples for fatigue and durability testing.

The manufacturer shall experimentally establish a stress-strain constitutive model.

To help assess and interpret the results of the computational simulations, the manufacturer shall establish (i.e. experimentally measure and statistically calculate) the fatigue life of the material (e.g. fatigue endurance limit for ferrous and titanium alloys, fatigue strength for nonferrous metals and alloys, such as nitinol, or constant life line for mean and alternating stresses/strains). These fatigue values shall be measured at the desired number of cycles for fatigue assessment (e.g. 400 million cycles). The use of material mechanical and fatigue characterization data from literature may be justified, however it is likely to not be acceptable because of the potential differences provided in H.2.3.

NOTE See ASME V&V 40[9] for the requirements on the verification and validation of the computational model.

7.2.5 Component corrosion assessment

An assessment of the corrosion resistance of all constituent metallic materials comprising the cardiac occluder system shall be conducted. It is well established that metal corrosion potential can be sensitive to variations in manufacturing processes (e.g. heat treatment, chemical etching, electropolishing, coating) and device loading and deployment with the delivery system. Therefore, the corrosion resistance shall be characterized using the finished conditioned component.

The manufacturer shall provide rationale for the selected test methods and justify that all corrosion mechanisms and conditions have been considered through testing or theoretical assessments (e.g. potential for fretting damage in designs that allow micromotion between contacting components). Suggested guidelines are provided in Annex F.

Corrosion assessment includes, but is not limited to, evaluation of test results, review of literature and consideration of the historical clinical performance of the material(s) under assessment.

For indications that an occluder interacts with another metallic device, the manufacturer shall consider all interactions with the pre-existing device in terms of corrosion potential (e.g. galvanic corrosion, fretting corrosion).

NOTE See ASTM F1801[12], ASTM F2129[15], and ASTM F3044[17].

7.2.6 Visibility

The ability to visualize the implanted device and delivery system during delivery, deployment and during/after delivery system withdrawal, using the manufacturer's recommended imaging modality in the labelling (e.g. fluoroscopy, TEE, ICE, MRI, CT, echocardiography) shall be evaluated.

NOTE See ASTM F640[11].

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7.2.7 Visual inspection

The device shall be inspected to ensure it meets visual criteria established by manufacturer.

7.2.8 Dimensional verification

The manufacturer shall demonstrate that the device dimensions conform to design specifications.

7.2.9 Device MRI compatibility

The manufacturer shall evaluate the safety and compatibility of the implant with the use of MRI and include that information with its labelling. If the cardiac occluder is intended to be implanted into or adjacent to a pre-existing implant, testing shall consider the effects of the pre-existing implant.

ASTM F2052, ASTM F2119, ASTM F2182, ASTM F2213, and ASTM F2503 shall apply.

7.2.10 Simulated use assessment

The ability to permit safe, consistent and accurate delivery and deployment of the transcatheter cardiac occluders within the intended implant site shall be evaluated using a clinically relevant model that simulates the intended use conditions. This assessment will include all elements of the transcatheter cardiac occluder system required to facilitate the implantation procedure (e.g. delivery, positioning, repositioning, deployment, and retrieval). The model shall consider anatomical variation with respect to delivery pathway and intended implant site as well as physiologic factors (e.g. test fluid, tissue compliance, temperature effects). In the case of deployment of the cardiac occluder within or adjacent to a pre-existing prosthetic cardiac device, the model shall consider the dimensions and conditions (e.g. endothelialisation, tissue encapsulation, calcification) of the existing device.

7.2.11 Usability engineering process

Evaluate the usability of a medical device as it relates to safety in accordance with IEC 62366-1.

7.2.12 Design- or procedure-specific testing

Design specific testing shall be considered to assess additional failure modes identified by the risk assessment that might not have been already addressed. In some cases, design specific testing can have direct implications for the overall structural lifetime of an occluder component, and additional tests may be required. Annex I provides examples of potential hazards of cardiac occluder systems to inform design specific testing. Examples of additional device design evaluation requirements are presented in Annex L.

7.3 Preclinical in vivo evaluation

7.3.1 General

General requirements of ISO 14630 shall be considered.

7.3.2 Overall requirements

Preclinical studies to enable acceptably safe clinical investigations shall precede initiation of clinical investigations. An in vivo animal test programme shall be conducted for new or modified devices to investigate those risks and aspects of safety and performance that cannot be fully evaluated from in vitro testing or other available data regarding cardiac occluder device delivery, deployment and imaging characteristics and cardiac occluder device safety and performance. The preclinical programme design shall be based on the risk analysis. This design shall consider device safety and, when feasible, performance.

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The choice of animal model (e.g. species, diseased or non-diseased, age, weight), study duration, device size and sample size shall be justified and documented. The relevant anatomical and physiological similarities, differences and limitations of the animal model compared to the humans for the device use shall be included in the animal model justification. The use of alternative implantation sites, alternative implantation techniques and acute as well as chronic studies can be justified to accommodate specific cardiac occluder design features and species-specific anatomic differences.

Anatomic species differences and use of diseased or non-diseased animal models shall be considered when interpreting results from preclinical in vivo testing alone. Diseased animal models exist for PDA, ASD, and, VSD (e.g. see References [34] and [48]). If preclinical in vivo evaluation is determined to not be required, the justification shall be documented.

The preclinical in vivo evaluation shall:

a) Assess delivery, deployment, implantation procedure and imaging characteristics of the cardiac occluder system. Consideration shall be given, but not limited, to the following items:

   1) ease of use of the cardiac occluder system (e.g. assembly, flushing, advancement/pushability, torquability, positioning, deployment, recapturability, and withdrawal);

   2) post-implantation changes in shape and structural components of the transcatheter cardiac occluder;

   3) imaging characteristics for placement and effectiveness of occlusion and impact on physiology (e.g. either device radiopacity or echo-opacity, or both; quantity of contrast used);

   4) migration or embolization of the cardiac occluder;

   5) interaction with surrounding anatomy, for example, iatrogenic atrial-septal defect, and catheter induced injury such as an air embolism, a perforation, a dissection, a vascular constriction or spasm, or endothelial cell disruption;

   6) ability to resist unintended deformation of the access and delivery system (e.g. kink, stretch);

   7) ability to maintain haemostasis.

b) Evaluate the extent to which the safety and performance of the cardiac occluder system reflect the intended clinical use; the following items shall be evaluated, if applicable:

   1) ability to prevent residual shunt, device embolization, pericardial effusion, device-related thrombus, unstable device placement, and interference with other unintended cardiac anatomies;

   2) cardiac occluder integrity during the follow-up period.

c) Assess the in vivo response to the cardiac occluder. Consideration shall be given, but not limited, to the following items:

   1) healing characteristics of the device surface (including endothelialisation), tissue integration of device into the endocardium and healing on the occlusion side of the device (LAA cavity);

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

   3) haemolysis;

   4) thrombus formation on the exposed blood flow surfaces;

   5) emboli of material from the implant site, delivery device or cardiac occluder and device interactions; emboli may be observed in distal organs such as brain and kidneys;

   6) infarction in distal organs such as brain and kidneys;

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7) migration or embolization of the cardiac occluder or deformation over time of the cardiac occluder;

8) biological response (e.g. inflammation, thrombosis, rejection, changes in electrical activity, other unexpected interactions with tissues);

9) interaction with surrounding anatomical structures, for example, transmural erosion of myocardium, development of fistula tracts, formation of jet lesions from incomplete acute sealing or loss of seal over time, compression necrosis, ostial fibrosis, changes in cardiac rhythm; changes in valvular regurgitation; changes in blood flow within surrounding vasculature; and changes in atrial or ventricular volume, and either compliance or contractility, or both.

d) Use the final design of the cardiac occluder system. Where applicable, the system shall be either prepared, deployed, recaptured, retrieved, repositioned or removed, or all and imaged using the same procedures as intended for clinical use. Consideration shall also be given to effects of maximum allowable conditioning steps (e.g. maximum sterilization cycles, maximum loading cycles, maximum time the implant is constrained within the delivery sheath, maximum retrieval and repositioning events if indicated in the IFU).

1) If needed, ancillary studies can be conducted to evaluate unique design and delivery aspects of the device.

2) The manufacturer shall justify any modifications to the device or system, such as device scale, that can be required for implantation in the animal model and address the impact of the modifications on the interpretation of results.

e) Investigate the cardiac occluder system in positions and physiological situations for which it is intended (e.g. septum, LAA, membranous or muscular, congenital or acquired, acute or chronic; see References [25], [34] and [48]); if species-specific anatomic features or the use of a non-diseased animal model confound the ability to evaluate the cardiac occluder in positions for which it is intended, provide a justification for implantation in an alternative site or the use of alternative implantation procedures.

f) Subject a comparably sized reference cardiac occluder to identical anatomic and physiological conditions as the test device.

g) Perform the preclinical in vivo evaluation by appropriately experienced and knowledgeable test laboratories under appropriate quality assurance standards (e.g. either Good Laboratory Practice or ISO/IEC 17025[50], or both).

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

7.3.3 Methods

Guidance on the conduct of in vivo preclinical evaluation and a series of tests which can be used to address the relevant issues is provided in Annex N. The intent of these studies is to mimic as closely as possible the clinical use of the cardiac occluder system (e.g. delivery, deployment, imaging) and to assess the in vivo response with respect to performance and safety. It is recognized that adverse events arising after occluder implantation can be attributed to either the implanted cardiac occluder, the procedure, or the environment into which it is implanted, or all, including interactions among these. Therefore, serious adverse events arising during or after cardiac occluder implantation shall be analyzed and interpreted in order to identify the cause of the adverse event.

The investigator should seek to control as many variables as possible within each study arm (e.g. species, gender and age). Animals suffering from periprocedural complications may be excluded from the group of study animals, but they shall be reported.

For all studies, the specified duration of the observation period of the animals shall be justified according to the parameter(s) under investigation in each study protocol. For long-term studies, the observation period shall be appropriately justified in each study protocol but shall not be less than (90 ± 5) days.

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The number of animals used for implantation of test and reference cardiac occluders shall be justified. For the long-term study of the final design of the cardiac occluder system, a minimum of six animals shall be assessed at the terminal endpoint, unless otherwise justified by risk assessment.

For survival studies, a post-mortem examination shall be performed (e.g. macroscopic, radiographic, histological) focusing on device integrity and delivery system/device related pathology. The report shall include this information from all animals that have been entered into the study.

The assessment shall provide at least the following:

a) animal health condition during the survival period, indicated by periodic observation of feed intake, excretion of urine and feces, signs of illness or injury, and interaction with pen-mates;

b) necropsy, including in situ evaluation of the cardiac occluder; tissue trimming and orientation shall be documented, including processing methods, plane of section and number of sections taken;

c) any detectable pathological consequences, including but not limited to: migration or embolization; post-implantation changes in shape of structural components; thrombo-embolic phenomena; endothelialisation; and either tissue disruption or inflammatory responses, or both, involving either the cardiac occluder or in the major organs (i.e. histopathology), or both;

d) any detectable structural alterations (macro- or microscopic or radiographic) in the cardiac occluder (e.g. damage, material degeneration);

e) 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;

f) delivery and deployment characteristics, including but not limited to ease of use, handling characteristics, imaging, sizing technique, deployment, recapturability, retrieval, repositionability and/or removal, if applicable;

g) serious adverse events (e.g. animal death, myocardial infarction, significant cardiac arrhythmias, embolization);

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

7.3.4 Test report

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

a) identification of each of the cardiac occluder system components used in the procedure (product description, model, serial number and other appropriate identification);

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

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

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

e) names of the investigators and their institutions along with information about the implanting personnel and the laboratory's experience with cardiac occluder implantation and animal care;

f) interpretation of data and a recommendation relative to the expected clinical safety and performance of the cardiac occluder system under investigation;

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g) for survival studies, the study pathology report shall include gross photographic and radiographic examination, histopathology findings and clinical pathology analysis (blood test) result, for each explanted cardiac occluder;

h) for survival studies, detailed necropsy reports for each animal in the study that includes an assessment of the entire body including such findings as thromboembolism or any other adverse effects putatively from the cardiac occluder;

i) a summary of all data generated from all animals during the course of the investigation shall be included; in particular, serious adverse events generated by evaluations described in Annex N, deviations from the protocol and their significance, shall be addressed.

7.4 Clinical investigations

7.4.1 General

The requirements of ISO 14155 shall apply. Clinical investigations shall be performed for new cardiac occluder systems and expanded indications for use. For modifications of an existing cardiac occluder 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. Appropriately sized and designed clinical investigations are recommended to allow an assessment of the effects design changes of a marketed device can have on the device's previously established safety and effectiveness and benefit-risk profile (e.g. novel blood-contacting materials or changes that affect the mechanical loading on the occluder).

Clinical investigations shall be designed to evaluate the cardiac occluder system for its intended use. The studies shall include an assessment of adverse events related to risks arising from the use of the cardiac occluder 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. Depending on procedure and expected timing of peri-procedural events, varying intervals can be justified. For occluders, a minimum duration for assessment of peri-procedural events can be from initiation of the index procedure to 30 days post-procedure or hospital discharge, whichever is later; a shorter duration can be considered if justified. The clinical investigation programme shall be designed to provide substantial evidence of acceptable safety and effectiveness to support the intended labelling for the device.

In accordance with ISO 14155, medical devices can undergo three general stages of clinical development based on the risk assessment. The phases of a clinical programme typically include a pilot phase (i.e. first in human clinical investigation, early feasibility clinical investigation and traditional feasibility clinical investigation), 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 or via other special access program (i.e. compassionate or emergency use) shall not be used as a substitute for any clinical investigational study. Prior to embarking on a pivotal clinical investigation, pilot phase studies (early feasibility or proof of concept clinical investigations) shall be considered to provide initial information regarding clinical safety and device performance. A scientific justification shall be provided if pilot phase studies are not to be undertaken. The information derived from the pilot phase may be used to optimize the cardiac occluder system (i.e. design of device and accessories), types and methods of access for implant, endpoint selection or modification, and patient selection prior to initiation of a larger clinical investigation following further pre-clinical testing.

A pivotal clinical investigation shall be designed to ensure:

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

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

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

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

a) ethical considerations may require a head-to-head comparison with alternative treatments or standard of care; randomized trials provide the highest quality scientific evidence and minimize bias;

b) randomized trial results may promote adoption of effective therapies.

For clinical investigations to serve as a basis for market approval, there shall be sufficient data to support the safety and effectiveness of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use. Safety and effectiveness of a device in the context of a market approval application are to be determined in part by weighing any probable benefits to health from the use of the device against any probable risk of injury or illness from such use of the device. These studies shall include a pre-specified statistical methodology, specific inclusion/exclusion criteria, use of accepted endpoint definitions, a rigorous method of collecting information on defined CRFs, a rigorous system to monitor the data collection and defined follow-up intervals. The appropriate use of imaging core laboratories and clinical events committees for adjudication and data safety monitoring boards should also be included.

7.4.2 Study considerations

The decision to use a medical device in the context of a particular clinical trial requires the residual risks and the anticipated benefits of the test device and procedure to be balanced against the known risks and benefits of alternative control therapies (see ISO 14971). A premarket investigation is a study carried out before market approval of the investigational device. A clinical investigation carried out following market approval, intended to answer specific questions relating to clinical performance, effectiveness or safety of a medical device when used in accordance with its approved labelling. The clinical investigation population can be influenced by the type of clinical development stage, for example, the pilot stage population may come from a sub group of the total target population for which the device is eventually indicated. However, by the time the pivotal stage is reached, the clinical investigation population should more closely mirror the target population. If marketed medical devices are being investigated for new indications, other than described in the approved labelling, requirements for pre-market clinical investigations apply. With cardiac occluder systems, device performance and those adverse events which are directly related to the device or procedure shall be measured to assess risk (e.g. tissue erosion, haemolysis, vascular injury, stroke or systemic embolization). Device and clinical performance including adverse events may also depend on factors other than the device itself, including:

a) patient comorbidities;

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

c) pathology-related tissue properties;

d) whether the achieved changes in anatomic pathology result in appropriate and sufficient physiologic changes to prevent or reverse expected progressive deterioration in cardiac function;

e) technical factors involved in delivery and implantation;

f) either appropriate selection of available sizes or shape configurations, or both;

g) the potential for adverse haemodynamic effect.

Refer to Annex I for more information about adverse events classification during clinical investigation.

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7.4.3 Imaging assessment

Imaging assessment is an essential aspect of the clinical investigation for patient selection, device placement or re-positioning, avoidance of procedural complications and patient follow-up. To ensure optimal anatomic evaluation, device access and position, functional assessment, and multiple imaging modalities (e.g. TEE, TTE, ICE, CT, MRI, fluoroscopy) can 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 approval shall be conducted before enrolment in collaboration with the independent core laboratory (see Annex P). Imaging endpoints and follow-up time points for discernment shall be specified and justified, and the follow-up shall be completed as specified in the CIP. See Annex J.

7.4.4 Study design

The CIP shall clearly define the objectives of the study and specify safety and effectiveness end points (see Annex I). The CIP shall specify either anticipated study-related adverse events, including device or procedure-related adverse events, or both, in accordance with Annex I and published definitions. The definitions of the outcome measures shall be consistent with those described in this document to allow comparability of other approved cardiac devices. The study design shall include a pre-specified statistical analysis plan and success criteria (e.g. new devices should be at a minimum non-inferior to standard of care).

Studies should employ appropriate measures to minimize bias where possible. Study designs can vary depending on the purposes of either the assessment or the technology (novel technology versus modification to well-established device), or both. Study populations shall be representative of the intended post-market patient population, including etiology 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 will end at the time of the withdrawal. However, depending on local requirements, additional follow-up can be obtained. All subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) shall be accounted for and documented. If a subject discontinues participation in the clinical investigation, the reason(s) shall be recorded. The investigator can use existing data and ask for the subject's permission to collect follow-up data about his/her status or condition including information about device clinical performance, effectiveness or safety. If permission is obtained, the relevant data shall be included in the clinical investigation report.

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 CRFs (data collection forms) shall be standardized across institutions and investigators.

Study monitoring shall be conducted in accordance with ISO 14155.

7.4.5 Explant analysis

Explant analysis is a vital part of device evaluation. The need for this analysis shall be described in the patient information sheet and consent for explant shall be obtained at the time of enrolment. Devices explanted or obtained at autopsy shall be assessed by a pathologist with appropriate medical device pathology training/experience, where appropriate. This can be a cardiovascular pathologist if he/she has device pathology experience. The results of analyses shall be reported in accordance with the CIP including operative or autopsy photographs, or photograph of retrieved device by transcatheter techniques or in situ (surgical or autopsy) and after explant. The CIP shall include an explant pathology protocol with detailed instructions for processing and evaluation by an independent pathologist (including operative or autopsy photographs). Device pathology analysis can require specialty plastics embedding which many hospitals are not equipped to perform. Where appropriate, collaboration with the manufacturer for instructions and, potentially, assistance for the return and processing of the explanted devices, should be considered. Whenever feasible, the explanted device shall be subjected to appropriate functional, imaging and histopathological investigations. In the event of subject death,

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valuable information about implanted devices can be obtained by autopsy, which should be encouraged whenever possible.

NOTE See ISO 12891-1[1] and ISO 12891-2[2].

7.4.6 Pilot study considerations

If a pilot stage is necessary, an exploratory clinical investigation(s) will evaluate the limitations and advantages of the medical device and is commonly used to capture preliminary information on a medical device (at an early stage of product design, development and validation) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal clinical investigation. This stage includes first in human and feasibility clinical investigations. Exploratory clinical investigations might not require pre-specified statistical hypotheses, although the design of the clinical investigation and the interpretation of the outcome can be more straightforward if statistical considerations are provided in the CIP.

Given the exploratory nature of pilot phase studies for devices still in development, the following safeguards are essential:

a) patient selection shall be a shared decision process between physician and patient that takes into account the best scientific evidence available, as well as the patient's values and preferences;

b) the consent process shall inform the subjects of the pilot phase nature of the study and what that means (e.g. clear language stating that the device together with the procedure has not been evaluated for safety or effectiveness and that the patient is among the first in the world to be treated with this device) and alternative options including other approved devices;

c) oversight of the study safety shall be performed by a Data Safety Monitoring Board (DSMB) or an independent medical reviewer;

The following additional considerations can also apply for pilot phase studies:

a) pilot phase studies 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) limitations on rate of enrollment may be applicable based on risk assessments (e.g. evaluation of acute outcomes after each patient and before treating the next patient);

c) a Clinical Events Committee (CEC) shall be used for adjudication of adverse events;

d) use of imaging or other appropriate core labs should be considered;

e) re-evaluation of risk/benefit profile as appropriate based upon study outcomes as they become available.

7.4.7 Study endpoints

The choice and timing of primary and secondary study endpoints shall be driven by the study objectives, the pathology, the patient population, the technology, the post-operative medical treatment (e.g. antithrombotic medication) and anticipated risks. Endpoints shall include safety and effectiveness such as time-related safety, acute mortality and longitudinal survival, quality of life, symptomatic and functional status, and device and procedural success. Other tertiary or descriptive endpoints should be considered relative to the technology. Guidance for clinical investigation endpoint selection is provided in Annex K.

7.4.8 Ethical considerations

Although novel cardiac occluder systems can have been extensively tested in vitro, by computer simulation and by implantation in animals, human studies are essential, yet carry significant risk to patients, especially in first in human studies. Diseased human hearts are structurally and functionally

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different from healthy or diseased animal hearts. Further, the investigators who implant the device will be subject to learning curves. Even if similar devices have been previously implanted successfully, differences in either design and materials, route of access, deployment or anchoring techniques, or all, can impose unforeseen hazards.

The choice of patients to receive the first implants of a novel technology places responsibility on both manufacturers and investigators and raises important ethical issues. Choice of objective and skilled investigators who will implant the new device is equally important. Relevant guidance on conflict of interest has been provided by regulatory agencies or other organizations (Baim, 2007[23], Lo, 2009[33]; Qaseem, 2019[41]). A rigorous process for disclosure of interests and management of conflicts of interest is essential for management of conflict of interest and guidance statements from national and international organizations should be followed. Manufacturers shall not offer financial incentives to the institution or investigators to implant the device. Compensation of patients for the costs for participating in the clinical investigation shall be limited to an appropriate amount in line with ISO 14155 and shall not be so large as to encourage patients to participate.

See also 7.4.10 for additional detail for site and investigator selection considerations. Ethics Committee/ Institutional Review Board approval shall be obtained for both pilot phase and pivotal studies.

7.4.9 Pivotal studies: Distribution of subjects and investigators

In the pivotal stage, one or more confirmatory clinical investigations can be conducted to provide the information necessary to evaluate the clinical performance, effectiveness or safety of the investigational device. A confirmatory clinical investigation shall be adequately designed with a pre-defined hypothesis for the primary endpoint(s) and a pre-specified sound statistical method for the analysis laid out in the CIP.

The clinical investigation population can be influenced by the type of clinical development stage, for example, pilot stage population may come from a subgroup of the total target population for which the device is eventually indicated. However, by the time the pivotal stage is reached, the clinical investigation population should more closely mirror the target population.

7.4.10 Site qualification and training requirements

Clinical investigations of cardiac occluders shall be conducted in institutions with appropriate facilities, case-load and case-mix and by investigators with appropriate experience, skills and training (see Annex P). The available scientific guidelines should be followed to ensure required competencies, expertise and procedure-specific skills. Patients should be evaluated by a multidisciplinary team when intervention with a cardiac occluder is considered. Learning new techniques shall take place through mentoring and proctoring to minimize the effects of the 'learning curve' (see References [24], [26], [30], [32], [37], [39] and [46]).

The procedures shall be performed in an adequately equipped cardiac catheterization laboratory or hybrid room, properly sized to accommodate anaesthesia and imaging equipment and have a non-portable C-arm system for fluoroscopic imaging and continuous haemodynamic monitoring. The room shall have the equipment to manage cardiac perforation and tamponade, device or air embolization, and other serious adverse events. Large sheaths and catheters, transseptal puncture kits, different wires, snares, and pericardiocentesis equipment shall be readily available. Site readiness for the procedure necessitates not only a knowledgeable operator but also a thorough team understanding of the procedure and of the individual role of each member of the team.

7.4.11 Study population

Clinical investigations shall be designed to include enough subjects, investigators, and institutions to be representative of the intended patient and user populations. The design shall include consideration of and justification for such aspects as disease etiology, disease severity, gender, age (e.g. adult, pediatric) 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

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for any expected differences in standard of care or patient outcomes based upon the geographic distribution of the intended patient or user populations. The CIP shall specify and justify the planned number of institutions (including geographical distribution), the minimum and maximum number 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:

a) sites:

   1) suitable distribution of sites;

   2) access to the defined patient population;

   3) presence of a local or central IRB/EC;

   4) qualified centres, following the guidelines on operator and institutional requirements published jointly by the professional societies (see References [26] and [30]);

   5) involvement of a multi-disciplinary heart team in patient selection;

   6) expert imaging with accredited operators and facilities (see also Annex J) in agreement with core lab specified image acquisition and transmission protocols;

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

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

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

   10) experience with investigational device clinical studies;

   11) acceptable results of previous regulatory inspections;

b) clinical investigators:

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

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

   3) prior clinical research experience;

   4) avoidance of competing studies (e.g. to avoid selection, channelling biases); minimizing potential conflict of interest.

7.4.12 Statistical considerations

The manufacturer is responsible for selecting and justifying the specific statistical methodology used. The size, scope, and design of the clinical investigation shall be based on:

a) the intended use of the device;

b) the results of the risk analysis;

c) measures that will be evaluated;

d) the expected clinical outcomes.

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A prospective randomized controlled trial, assessing superiority or non-inferiority as appropriate, may be considered to minimize bias. Depending on the scope and objectives of the clinical investigation, other designs (e.g. blinding, sham controls) can be appropriate.

The decision to use a medical device in the context of a particular clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure in comparison with the risk and anticipated benefits of alternative procedures or therapies (see ISO 14971). If a comparable device is on the market, the study control may be the comparable device or another active comparator, such as surgery or medical therapy. If a comparable device is not on the market, randomization against an appropriate active comparator should be used. If the study uses a non-inferiority design, the non-inferiority margin shall be justified and, to the extent feasible, based on prior data from comparable devices.

For pivotal studies (single-arm or concurrent control), the sample size shall be justified and shall be sufficient to enable assessment of the safety and performance or effectiveness endpoints of the cardiac occluder system in the intended populations.

7.4.13 Sample size

The sample size shall be sufficient to enable assessment of the clinical performance of the cardiac occluder device as well as to quantify the associated risk.

The number of patients in a clinical investigation shall balance the need for a reliable answer to the questions addressed whilst minimising the exposure of subjects to risk. In certain circumstances, the objectives of the investigation can involve a comparative group which will influence not only the design but the appropriate sample size and subsequent investigation analysis. The usual method for determining the appropriate sample size for a pivotal investigation requires:

— specification of a primary endpoint(s);

— hypotheses;

— type 1 error (conventionally 5 % or less for a 2-sided test or 2,5 % or less for a 1-sided test);

— power (conventionally 80 % or above);

— attrition (conventionally 5 %).

When using devices in less common patient populations (e.g. paediatric, adult congenital), different statistical considerations may apply and shall be defined and justified.

7.4.14 Duration of study

The protocol shall specify total expected duration of the clinical investigation and expected duration of each patient's participation.

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 7.4.16.6). 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.

7.4.15 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 shall only include patients who are willing and able to participate in the follow-up requirements.

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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. vascular anomalies, congenital defects, paravalvular leaks, prosthesis endoleaks);

c) severity of defect using standard grading criteria where available;

d) symptomatic versus asymptomatic patients;

e) co-morbid conditions (e.g. MI, coronary or peripheral artery disease, previous infective endocarditis, rheumatic heart disease, degenerative neurological disorders, frailty, previous cardiac interventions, prior stroke or systemic embolism, previous haemorrhagic/bleeding events, chronic kidney disease, hematologic disorders, chronic lung disease);

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

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

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

i) tolerance for procedural or post-procedural anticoagulation or antiplatelet regimens;

j) life expectancy;

k) device or procedure specific anatomical considerations (e.g. congenital defects, access site conditions, device location, tolerance for required imaging);

l) pregnancy or breastfeeding contraindicating the procedure; contraceptive measures for subjects of child-bearing age;

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

7.4.16 Clinical data requirements

7.4.16.1 General

Clinical data, including adverse events, shall be recorded for all subjects in the study as required by ISO 14155. Consideration and appropriate justification shall be made for the collection and analysis of site reported versus core laboratory adjudicated data.

7.4.16.2 Baseline

The following data shall be collected based on the patient population being studied and the device indication:

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

b) baseline information (e.g. weight, height, blood pressure, CHA2DS2-VASc score, HAS-BLED, haemolysis evaluation, BNP, NT-proBNP);

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

d) cardiovascular diagnosis 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;

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e) NYHA functional class, and frailty and quality of life indicators should also be considered;

f) previous relevant cardiac interventions (i.e. surgical or non-surgical);

g) echocardiographic and other relevant imaging data to provide cardiac haemodynamic, geometric and functional information (e.g. ventricular function), and to characterize the defect and to assess implant site and the size of the orifice or leakage site, and determine the presence or absence of intra-cardiac clot; relevant imaging data for assessment of access and delivery approach;

h) blood test to assess hepatic, cardiac and renal status;

i) haematologic or coagulation profile.

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

7.4.16.3 Peri-procedure data

The following data shall be collected:

a) name of operator(s);

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

c) date or time of procedure;

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

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

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

g) list of procedural devices (e.g. guidewires, catheters, introducers);

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

i) mechanical circulatory assist devices (e.g. pre, intra, post-procedural), and associated parameters (e.g. ACT, core body temperature, cardiopulmonary bypass time, inotropic support, cardiac arrest time);

j) imaging modalities (e.g. fluoroscopy, TEE, TTE, ICE, CT, MR), including fluoroscopy time and total radiation dosage, in accordance with the applicable radiation protection standards (see Reference [45]);

k) any changes from original diagnosis;

l) cardiac occluder system (e.g. type, models, sizes, and serial numbers);

m) any concomitant interventions or procedures (e.g. PCI, cardiac ablation);

n) elements of procedure, including any adjunctive procedures performed (e.g. contrast volume);

o) access site and technique (e.g. transfemoral);

p) assessment of implant site and other relevant sizing measure of patient;

q) implant position in relation to surrounding cardiac structures;

r) size, type, implant date and failure mode of previously implanted prosthesis, if applicable;

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

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

u) procedural complications, including vascular complications, cardiac perforations, malignant arrhythmias, cardiac valvular damage, device embolization, need for iatrogenic ASD closure (from transseptal access), bleeding, prosthetic valve interference, coronary obstruction, and other serious adverse events, that require interventional or surgical conversion;

v) evaluation of cardiac occluder function by either echocardiography or other relevant imaging and haemodynamic modalities, or both, as defined in the CIP; at a minimum, any residual device-related leakage shall be documented.

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

7.4.16.4 Follow-up data

At a minimum, follow-up data shall be collected between 30 d and 60 d, at one year, and annually thereafter until the investigation is completed. Physical examination of patients is recommended. The following evaluations shall be performed at all follow-up assessments unless an adequate risk analysis justifies a less frequent interval. Depending on the investigational design, additional data collection times can be appropriate.

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

The following data shall be collected:

a) date, method (in person, telephone), location and type of health care professional performing follow-up (e.g. investigator, primary care physician, nurse);

b) results of physical examination, if applicable, including specific parameters to be reported;

c) functional assessment (e.g. 6 Minute Walk Test, peak VO_2), where appropriate;

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

e) an imaging study shall be performed on all patients within the first 6 months;

f) haemodynamic evaluation by Doppler echocardiography, or other relevant methodology (the methodology chosen should be consistent for consecutive studies, see Annex J);

g) heart rate, rhythm and conduction abnormalities;

h) tests for haemolysis (e.g. plasma-free haemoglobin); other blood tests may be indicated;

i) status and duration of either the anticoagulant or antiplatelet therapy, or both (e.g. INR history), if applicable, including details of the type of medication used (e.g. vitamin K antagonists, direct thrombin inhibitors, Factor Xa inhibitors);

j) adverse events as specified in Annex I;

k) date and reason for reintervention (e.g. surgical, percutaneous), where appropriate;

l) date and cause of death, where appropriate;

m) explant analysis and autopsy report, if performed; the autopsy report shall include any evidence of organ damage from thromboembolism.

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

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7.4.16.5 Clinical investigation analysis and reporting

The clinical investigation report shall comply with ISO 14155. The clinical investigation report shall include information on all subjects for whom implantation was planned (i.e. the "intent-to-treat" population). For randomized studies, the groups shall include all randomized subjects, even those who did not receive the implant. Additional analyses shall be performed on the subjects who actually received the implant. Justification shall be provided for those who were randomized but did not receive an implant.

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

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

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

c) efforts shall be made to ascertain the cause of death, including contact with local physicians if the patient died elsewhere, obtaining details of any investigations performed shortly before death, and autopsy data and explant data if available; reliance on national healthcare databases alone to record that death has occurred might not be sufficient; a high percentage of unknown cause of death may raise suspicion of device-related deaths.

7.4.16.6 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. In cases when the device addresses a critical unmet need (e.g. rare diseases, congenital conditions), it may be allowed to collect effectiveness data in the pre-market and post-market phase.

The initial cohort of patients included in pre-market clinical investigations shall continue to be followed to a minimum of two years in the post-market setting. These patients are the best source of valid long-term data because they will have been extensively studied in the pre- and peri-operative periods with full documentation, and because overall mortality and adverse event rates can be calculated. Reasons for removing individual patients from longer-term follow-up shall be documented. To facilitate prolonged follow-up and avoid the need for re-consenting patients, informed consent that includes details regarding the planned duration of follow-up in the post-market period shall be obtained at the time of initial clinical investigation consent. For devices at risk for late erosions, this complication shall be reported systematically to allow determination of the device safety profile.

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. When deemed appropriate, this shall be performed in a prospectively designed PMCF study and a methodology shall be employed to minimize bias in patient selection (e.g. use of representative sites with all-comers consecutive enrolment). In addition to collection of device performance data in post-market studies, follow-up using various registries and administrative datasets can be useful for longer term follow-up.

Follow-up shall be as complete as possible avoiding retrospective self-reporting and reports shall 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, pre-use justification regarding the registries' usefulness for the specific device and procedure outcomes of interest shall be provided along with assessments of expected data reliability and relevance based on historical registry uses. In addition, there should be independent verification that all consecutive patients are entered and that all receive the same type of follow-up at each site. Planned linkages among various registries or administrative dataset sources may provide more robust long-term follow-up and shall be thoroughly described if planned. Data from

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registry and other specified dataset sources shall be regularly reviewed, and alert mechanisms should also be in place to trigger additional safety reviews based on pre-specified criteria.

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

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

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

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

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

d) follow-up shall include physician examination of the patient wherever possible and any relevant clinical assessments; a structured imaging protocol shall be recommended; 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 emphasized in 7.4.16.5.

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Annex A
(informative)

Rationale for the provisions of this document

A.1 Rationale for risk-based approach

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

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

The manufacturer should strive for continuous improvement in device design as well as test methodologies that can ensure safety and effectiveness of a device under variable operational environments, with less reliance on years of patient experience for evidence of performance or effectiveness.

To assure favourable risk to benefit for medical devices, a risk management process is required. New risks can be introduced or detected throughout the product lifecycle, and risks that become apparent at one point in the lifecycle can be managed by action taken at a completely different point in the lifecycle. For this reason, risk management needs to be included throughout the lifecycle from its initial conception until its ultimate decommissioning and disposal.

A.2 Rationale for preclinical in vivo evaluation

The overall objective of preclinical in vivo evaluation is to test the safety, and in some cases, performance of the cardiac occluder system in a biological environment with the closest practically feasible similarity to human conditions.

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

No single uniformly acceptable animal model has been established. Therefore, the animal model(s) selected should be properly justified to ensure the highest degree of human compatible conditions for the cardiac occluder system pertinent to the issues being investigated. Since chronic studies are conducted to elucidate delivery system and cardiac occluder performance, biological responses, structural integrity, and related cardiac pathology, it is preferable to undertake this chronic testing of the implant in anatomical positions for which it is intended. Modifications to the anatomical structures

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in the preclinical in vivo animal model may be necessary based on how the cardiac occluder implant configures to the surrounding anatomy and meets its intended purpose post-implantation.

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

A.3 Rationale for design verification and design validation testing

The purpose of design verification and validation testing is to demonstrate that the medical device meets the required design specifications and that the design specifications conform with user needs and intended use(s). Verification and validation testing includes materials testing, preclinical bench testing, preclinical in vivo evaluation, and clinical investigations. The tests specified herein do not purport to comprise a complete test programme; a comprehensive test programme for the cardiac occluder device should be defined as part of the risk assessment activities. Where the manufacturer's risk assessment concludes that the safety and effectiveness will be better demonstrated by other tests or by modifying the test methods included in this document, the manufacturer should include in the risk assessment a justification of the equivalence or superiority of the alternative test or test method.

While an extensive design verification and validation process may be required for new devices, a limited scope may be justifiable for a modification to an existing cardiac occluder device design or manufacturing method. The risk analysis should define the scope of the verification and validation, with consideration of the current state of the art.

A.4 Rationale for imaging assessment

Echocardiography and fluoroscopy are presently accepted as practical and available methods for evaluating human cardiac function and the function of cardiac occluder devices; other imaging modalities (such as CT, and cardiac MRI) are complementary. The accuracy of these diagnostic procedures depends upon the skill of the operator. Therefore, all investigating institutions involved in the clinical evaluation of a specific cardiac occluder device should employ the same imaging protocol to acquire and interpret images (see Annex I).

A.5 Rationale for clinical investigation reporting

The purpose of the clinical investigation is to determine whether a cardiac occluder system functions as intended, with complication rates within clinically acceptable performance criteria, based on published literature or a control group.

The clinical investigation of a cardiac occluder device requires documentation of specified complications (see Annex I). A new or modified cardiac occluder device should perform as well as existing devices or the current standard of care. Where appropriate, randomised clinical trials should be conducted comparing the cardiac occluder device against other appropriate cardiac occluders, therapeutic procedures or medical therapy. The clinical evaluation typically requires formal statistical evaluation of the clinical data in addition to descriptive statistics. Statistical evaluation methods and assessment criteria of clinical data can be different between the populations studied, including paediatric and adult study populations. Complications will be reported and evaluated as part of the overall performance evaluation. In order to establish long term safety and performance of cardiac occluders, post-market surveillance is also important.

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

Sizing may be a relevant parameter for some cardiac occluder devices, while some implants may be configurable in the anatomical location in some way beyond just size designations. The manufacturer should provide clear instructions (along with either special handling conditions, warnings, or

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precautions, or all) on how to deploy the implant in the intended anatomical location to ensure optimal functionality. Any changes and interactions that may occur in the surrounding anatomy during the positioning and after implantation should be presented in the instructions for use.

A.7 Rationale for usability or human factors engineering

Instructions for use and training are important and helpful safety features but they may not always ensure that a user interface facilitates correct use. Manufacturers incorporate usability/human factors engineering into their overall product development process to identify, assess and mitigate risks associated with correct use and use errors. Following this process allows manufacturers to improve device designs to ensure not only functionality, but also usability. The usability engineering of the user interface to achieve adequate usability requires a different process and skill set than that of the technical implementation of the user interface design. For a broader perspective, see IEC/TR 62366-2[6]. It includes usability as it relates to safety, but also includes how usability relates to attributes such as task accuracy, task completeness, task efficiency and user satisfaction.

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Annex B
(informative)

Transcatheter cardiac occluder hazard analysis example

B.1 General

As part of the requirements of risk management per ISO 14971, the manufacturer shall compile documentation on known and foreseeable hazards associated with the cardiac occluder system in both normal and fault conditions. Reasonably foreseeable sequences or combinations of events that can result in a hazardous situation shall be considered and the resulting hazardous situation(s) shall be recorded. For each identified hazardous situation, the associated risk(s) shall be estimated using available information or data.

Table B.1 is an example that is intended to demonstrate the linkage among a few potential hazards, foreseeable sequences of events, hazardous situations and harm for cardiac occluder systems. The example shown is not intended to be inclusive or applicable to all occluder applications. It is meant to stimulate thinking of "where can things go wrong" (see also ISO 14971:2019, Annexes C and E) and to provide an example of structured hazard analysis for cardiac occluders. Other elements commonly considered in hazard analysis include, but are not limited to, biocompatibility, durability, corrosion, visibility, sterility, ability to deploy and withdraw, ability to seal, and MRI safety.

This example combined with probability of occurrence and severity of harm analysis typically leads to risk mitigation activities, such as design changes, updated product specifications and associated test methods to develop a medical device with acceptable residual risks.

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Table B.1 — Example hazard analysis for cardiac occluder systems

Hazard	Foreseeable sequence of events	Hazardous situation	Harm	Risk control measures	Verification of effectiveness of risk control measures
Inadequate labelling of intended use	The labelling information is confusing in that it is unclear whether the label states the unconstrained device diameter or the diameters of the occlusion to cover. The device selected was too small.	Device embolization	Embolic event leading to aortic occlusion Death	Implant diameter (unconstrained) Maximum radial expansion force Labelling content DFU/training	Design validation Usability evaluation
	The labelling information diagram shows only the smallest size occlusion. A device that is too large is implanted.	Excessive radial force	1) Thromboembolic event 2) Haemolysis 3) Heart failure 4) Rupture 5) Pericardial effusion	Labelling content DFU/training	Design validation Usability evaluation
Occluder changes the atrial blood flow	A thrombus is formed due to alteration of flow dynamics resulting from the interaction between the device and patient anatomy or physiology.	Thrombus emboli may occlude blood vessel.	Disabling stroke	Implant length at constrained use Labelling content	Design validation
Inappropriate occluder radial force	An occluder with insufficient radial force is implanted resulting in poor occlusion.	Residual leak or blood flow	1) Thromboembolic event 2) Haemolysis 3) Heart failure 4) Rupture 5) Pericardial effusion 6) Open heart surgery and associated injury.	Implant minimum radial force at labelled minimum constrained state Labelling content	Embolization force testing
	An occluder with excessive radial force affects the surrounding tissue.	Tissue erosion and rupture	Pericardial effusion Fistula	Implant maximum radial force at labelled maximum constrained state Labelling content	Radial force testing Design validation
Inappropriate occluder anchor tissue engagement	Low heat treatment temperature in manufacturing lead to poor anchor shape setting Anchor shape not identified in inspection Device deployed with minimal number of anchors well embedded Device rotates	Device migrates or embolizes from intended location Device does not provide adequate occlusion.	Aortic obstruction Death Thrombo-embolic event Disabling stroke Death	Implant fixation force	Embolization force testing
	The device anchors penetrate through tissue.	Anchors perforate tissue.	1) Pericardial effusion 2) Cardiac tamponade	Anchor dimensions	Design validation
Inappropriate delivery system profile	Large delivery system OD difficult to advance Physician effort to advance leads to vessel trauma	Trauma to vessel	1) Vessel dissection 2) Vessel perforation 3) Bleeding complications	Delivery system OD	Design validation
Inappropriate delivery system stiffness	Delivery system too stiff to track through tortuous anatomy	Delivery system perforates vessel	1) Vessel dissection 2) Vessel perforation 3) Bleeding complications	Material and design specifications	Track force testing Design validation
	The delivery system is not stiff enough to allow controlled access.	Unable to perform procedure	1) Prolonged procedure 2) Device kinking	Material and design specifications	Track force testing Design validation

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Annex C
(normative)

Packaging

C.1 Requirements

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

C.2 Containers

C.2.1 Sterile barrier system(s)

The cardiac occluder device, delivery system (if applicable), and accessories (if applicable) shall be packaged in a sterile barrier system(s). It should be readily apparent if the sterile barrier system has been opened, thereby informing the user that the sterility has been compromised.

C.2.2 Protective packaging

Each sterile barrier system shall be packaged in protective packaging (sales/storage package) to protect the sterile barrier system(s).

C.2.3 Shipping container

Each outer container, or number of outer containers (not necessarily of the same type), shall be packaged in a shipping container designed to protect the contents under normal conditions of handling, transit and storage.

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Annex D
(normative)

Product labels and instructions for use

D.1 Requirements

D.1.1 General

The labelling requirements of ISO 14630, ISO 20417, ISO 15223-1, and ISO 15223-2 shall apply.

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

D.1.2 Instructions for use

In addition to the requirements for the instructions for use in ISO 20417, instructions for use shall provide

— specific instructions for device preparation (e.g. de-airing, assembly on delivery system);

— specific instructions for implanting or using the device;

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

— the appropriate MR safety designation (MR conditional, MR safe, or MR unsafe) and if the medical device is MR conditional, provide the conditions for safe use in the MR environment;

— post-procedure recommendations regarding either patient follow-up or medication, or both;

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

D.1.3 Labels for medical records

The manufacturer may provide peel-off, self-adhering labels, or equivalent, with each cardiac occluder device that enables transfer of device information to the appropriate records. If provided, each label shall contain: the name or model designation, size or configuration, traceable number (e.g. serial, lot, batch) of the cardiac occluder device and manufacturer identification.

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

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Annex E
(normative)

Sterilization

E.1 General

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

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

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

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Annex F
(informative)

Corrosion assessment

F.1 Rationale

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

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

Corrosion assessment typically includes a variety of methods (e.g. electrochemical, metallic ion release). Standard corrosion tests developed by ASTM, NACE and ISO address the technical requirements specified in the test method but can be required to be modified to appropriately address conditions applicable to device applications. If a Standard is followed where no acceptance criteria are prescribed, the manufacturer shall justify the final acceptance criteria adopted.

NOTE See Reference [44].

F.2 Introduction

The corrosion mechanisms described below are often applicable to materials and conditions representative of implantable devices, although other mechanisms are possible. ASTM F2129[15] and ASTM F3044[17] are often used and are adequate to assess pitting and galvanic corrosion, respectively. Durability testing of complete devices is often used and adequate to assess crevice corrosion, fretting corrosion and corrosion fatigue.

F.3 Pitting corrosion

Pitting corrosion is a localized form of corrosion. It occurs when discrete areas of a material lose their passive state and undergo corrosion attack while the majority of the surface remains unaffected. The localized corrosion attack creates small craters (pits) which can either rapidly penetrate the material or provide stress concentration sites and contribute to failure, or both. Pitting of a material depends on multiple factors, including, but not limited to:

a) localized chemical or mechanical damage to a protective oxide film;

b) environmental chemistry factors that can cause breakdown of a passive film such as acidity and high chloride concentrations;

c) localized damage of a protective coating;

d) the presence of nonuniformities in the metal microstructure (e.g. non-metallic inclusions);

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e) surface finishing processes (e.g. electropolishing or passivation).

NOTE See Reference [42].

The assessment of the pitting corrosion susceptibility of the device is of relevance both for storage solution and in simulated in vivo conditions. Previous experience with similar devices can be referenced; however, it is necessary to show the surface chemistries between the comparative devices, as the materials, design and fabrication processes specific to the device under analysis can reduce or eliminate the applicability of the comparative device. For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment, electropolishing, and passivation; therefore, the pitting corrosion susceptibility of the finished nitinol support structure should be characterized.

Pitting corrosion can be assessed by electrochemical methods, such as potentiodynamic methods described in ASTM F2129[15].

NOTE See Reference [31].

F.4 Crevice corrosion

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

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

Literature citations or previous experience with similar devices can be relevant. However, as the presence of critical crevices is strongly related to device design, and the material passivity is affected by the specific fabrication processes, generic literature might not be applicable. Comparing surface chemistries and crevices can be helpful when applying previous experience with similar devices. Crevice corrosion may be assessed by using a physiologically relevant solution (e.g. PBS) for durability testing of the finished device and examining the device for crevice corrosion upon completion of the test.

F.5 Galvanic corrosion

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

If the device contains more than one type of metal, such as a support structure with marker bands, the manufacturer should demonstrate the design's resistance to galvanic corrosion. The risk of galvanic corrosion should be addressed at a minimum by theoretical methods, such as the Evans Diagram and ASTM G82[20]. Test methods described in ASTM F3044[17] or equivalent methods may be used. If overlapping of devices of dissimilar materials is expected during clinical procedures, then the potential for galvanic corrosion should be addressed.

F.6 Corrosion fatigue

Corrosion fatigue can be defined as a materials failure mechanism which depends on the combined action of repeated cyclic stresses and a chemically reactive environment. One example is that localized corrosion-deformation interactions on smooth surfaces act as crack initiation sites at thresholds lower

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than estimated from linear elastic fracture mechanics. The total damage due to corrosion fatigue is usually greater than the sum of the mechanical and chemical components acting separately.

NOTE See Reference [35].

ASTM F1801[12] outlines corrosion fatigue testing of standard material specimens for medical implant applications. Corrosion fatigue may be assessed as part of the durability assessment of the device or in separately designed corrosion fatigue test for the support structure component.

NOTE See Reference [29].

F.7 Fretting: Wear, corrosion and fatigue

Fretting is defined as small amplitude oscillatory motion, usually tangential, between two solid surfaces in contact. Fretting wear is wear that occurs as the result of fretting action. Fretting corrosion is the deterioration at the interface between contacting surfaces as the result of corrosion and slight oscillatory slip between the two surfaces, with or without the abrasive effects of corrosion product debris between them. Fretting fatigue is the process of crack formation at a fretting damage site, progressive crack growth, possibly culminating in complete fracture, occurring in a material subjected to concomitantly fretting and fluctuating stresses and strains. Fretting corrosion may be assessed as part of the durability assessment of the device or in separately designed fretting corrosion test for the support structure component.

NOTE See ASTM E2789[10].

F.8 Post-fatigue corrosion evaluation

After completion of durability testing, specimens should be subjected to detailed microscopic surface inspection for any evidence of corrosion. Pitting corrosion testing (i.e. cyclic polarization) after durability testing generally does not provide value over the direct evaluation of the corrosion of manufactured components.

For devices with potential corrosion modes such as crevice corrosion, galvanic corrosion, corrosion fatigue, or fretting, inspect devices after completing mechanical fatigue testing to assess if such corrosion has occurred.

NOTE See Reference [28].

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Annex G
(informative)

In vitro test guidelines for paediatric devices

G.1 Introduction and paediatric definitions

The majority of cardiac occluders used to treat congenital defects, such as ASD, VSD and PDA and some of the occluders apply to adult population, such as PFO and LAA occluders. The devices available in the market to treat congenital defects are designed to treat the paediatric population, but there is a lack of sufficient clinical literature on haemodynamic indications for paediatric population.

The paediatric population can be generally divided into five groups (newborn, infant, toddler, child, adolescent) as listed in Table G.1 (see Reference [49]).

Table G.1 — Paediatric definitions

Paediatric subpopulation	Proposed definition
Newborn	$0 < A < 30$ days
Infant	30 days $\leq A < 1$ year
Toddler	1 year $\leq A < 5$ years
Child	5 years $\leq A < 13$ years
Adolescent	13 years $\leq A < 22$ years
A : age	

G.2 Pulsatile flow test conditions

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

Paediatric subpopulation	Systolic duration %	Mean atrial pressure (systolic/diastolic)	Peak arterial systolic pressure/low diastolic	Beat rate beats/min	Cardiac output l/min
Newborn	50	N/A	85/45[1]	60, 150, 200	0,3; 1; 1,5
Infant	50	N/A	100/55[1]	60, 120, 200	0,5; 2; 3
Toddler	45	12 (10-14)[2]	110/60[1]	60, 100, 160	1,5; 3; 4,5
Child	40	16,3 (5-38)[3]	120/60[1]	60, 80, 140	2; 3,5; 5
Adolescent	35	N/A	135/65[1]	45, 70, 120	2, 5, 7

NOTE 1 Peak systolic represents 95 % of population from Figures 415-1, 415-2, *Nelson Textbook of Pediatrics 17th edition.* ISBN 0-7216-9556-6; edited by Richard E Behrman, Robert MKliegman, Hal B. Jenson, 2004.[51]

NOTE 2 Echocardiography in the Assessment of Left Atrial Pressure After Pediatric Heart Surgery: A Comparison Study With Measurements Obtained From Left Atrial Catheter Marc Figueras-Coll, MD1, Joan Sanchez-de-Toledo, MD, PhD2,3, Ferran Gran, MD1, Raul Abella, MD4, Santiago Perez-Hoyos5, and Ferran Rose´ s, MD1 g World Journal for Pediatric and Congenital Heart Surgery 2015, Vol. 6(3) 438-442. [52]

NOTE 3 Cardiology in the Young - Agarwal A, Lam S, Li H, Gorla SR, Sasaki N, Rusconi PG, Swaminathan S. (2018). Association of left atrial pressure with left atrial volume and N-terminal prohormone brain natriuretic peptide in children with cardiomyopathy. Cardiology in the Young 28: 1333–1337. doi 10.1017/S1047951118001312 Received: 2 May 2018Revised: 4 June 2018 Accepted: 24 June 2018 First published online: 31 July 2018. [53]

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

Paediatric subpopulation	Systolic duration %	Mean atrial pressure (max/min)	Peak arterial systolic pressure (max/min)	Beat rate beats/min	Cardiac output l/min
Newborn	50	UNK	UNK	60, 150, 200	0,3; 1; 1,5
Infant	50	11/2[1]	95 [2]/ UNK	60, 120, 200	0,5; 2; 3
Toddler	45	UNK	120 [2]/ UNK[2]	60, 100, 160	1,5; 3; 4,5
Child	40	UNK	UNK	60, 80, 140	2; 3,5; 5
Adolescent	35	UNK	38/19	45, 70, 120	2, 5, 7

UNK: unknown, values that cannot be found in the current literature.

NOTE 1 Relation of Right Atrial Volume, Systemic Venous Dimensions, and Flow Patterns to Right Atrial Pressure in Infants and Children Shivani G. Patel, MD, Peter Woolman, MD, Ling Li, MD, PhD, Mary Craft, RDCS,David A. Danford, MD, and Shelby Kutty, MD, PhD, MHCM* Pediatr Cardiol (2016) 37:558–567 DOI 10.1007/s00246-015-1315-1. [54]

NOTE 2 Right Ventricular Volume Characteristics in Ventricular Septal Defect THOMAS P. GRAHAM, JR., M.D., GERALD F. ATWOOD, M.D., ROBERT J. BOUCEK, JR., M.D., DYKES CORDELL, M.D., AND ROBERT C. BOERTH, M.D. AHA Journals pg 800 Circulation VOL 54, No 5, NOVEMBER 1976[55]

G.3 FEA/life analysis conditions

Table G.4 — FEA/life analysis conditions: Left side

Paediatric subpopulation	FEA peak differential pressure/CO mmHg/l/min	Life analysis cycle criterion equivalent years
Newborn	90/1,5	5
Infant	100/3	7
Toddler	110/4,5	10
Child	135/5	10 [a]
Adolescent	160/7	10 [a]

[a] See Reference [49], says 15 equivalent years, which comes from U.S. FDA.

Table G.5 — FEA/life analysis conditions: Right side

Paediatric subpopulation	FEA peak differential pressure/CO mmHg/l/min	Life analysis cycle criterion equivalent years
Newborn	40/1,5	5
Infant	40/3	7
Toddler	40/4,5	10
Child	35/5	10 [a]
Adolescent	40/7	10 [a]

[a] Reference [49] says 15 equivalent years, which comes from U.S. FDA.

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Annex H
(informative)

Fatigue and durability assessment

H.1 General

A cardiac occluder is expected to be durable for hundreds of millions of cardiac cycles, thus an accelerated approach is required to demonstrate device durability within a reasonable timeframe. A durability assessment of a cardiac occluder is an integral part of the device risk assessment, design verification and design validation. The durability assessment described in this annex provides an assessment of the likelihood of structural component failure as well as the integrity of the occlusive element of the device during in vivo operation.

H.2 Fatigue of the structural component

H.2.1 General

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

A fatigue assessment (see Figure H.1) consists of:

— determination of in vivo boundary conditions;

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

— either material fatigue strength or crack growth property determination, or both;

— fatigue safety factor or probability of fracture determination;

— component fatigue demonstration testing.

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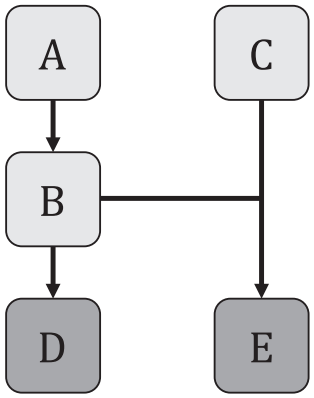

Key

A determination of in vivo boundary conditions
B structural component stress/strain analysis
C material fatigue strength determination (S-N or ε-N testing)
D component fatigue demonstration
E fatigue safety factor or probability of fatigue fracture

Figure H.1 — Example schematic of a structural component fatigue assessment

H.2.2 Determination of in vivo boundary conditions

The manufacturer should identify and justify the appropriate in vivo loading conditions to which the structural component(s) will be subjected. Device loading will depend on the implant site and device design, and may include, but is not limited to:

fluid mechanical loads such as

— differential pressures across the occluder; reference Annex O for guidance;

— transient shear stresses occurring during the cardiac cycle;

solid mechanical loads;

— contact loads with moving and deforming tissue;

— loads on components in tissue (e.g. hooks, barbs);

— loads due to contact with other devices;

— self-contact.

These loads may result in device deformations that may be modelled, if appropriate as

— radial dilatation and compression,

— torsion,

— bending,

— axial tension and compression, and

— linear or transverse compression (e.g. parallel-plate compression, localized compression).

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

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H.2.3 Structural component stress/strain analysis

A stress/strain analysis of the structural components should include the frame and anchoring mechanisms, if applicable. Other components such as sutures or coverings (e.g. fabric) should be considered for their reaction loads on the structural components.

Quantification of the stress/strain distribution within the structural component(s) is generally accomplished via the use of computational methods such as FEA. Critical inputs to a computational model are component geometry, selection of governing and constitutive formulae, material properties, and initial and boundary conditions to which the device will be subjected. The analyses should consider and establish the model input parameter sensitivities and uncertainties such as the effect of in-tolerance variations in dimensions of components and material specifications on the extremums in stress/strain and a calculated factor of safety, as appropriate.

The stress/strain analysis should account for the physiologic loading conditions to which the device will be subjected. It might not be feasible to simulate or test all relevant loading modes combined; however, any de-coupling or superposition of loading modes should be justified.

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

Stress/strain and fatigue analyses should be performed to determine the device size and configuration of highest likelihood of fracture for each planned durability test.

The stress/strain history of the device should include, but is not limited to:

— stress/strain condition of materials used for fabrication;

— device fabrication;

— crimping or loading onto or into the delivery system;

— deployment;

— retrieval and re-deployment, if applicable;

— physiologic loading conditions.

Symmetry boundary conditions may be used to reduce the computational model size when appropriate.

The constitutive model for each material used in the stress/strain analysis should account for either any superelasticity, plasticity, rate-dependent, temperature-dependent or non-linear material behaviour, or all, as appropriate. Constitutive models should be based on testing of material that is representative of the actual structural component, including material processing and environmental exposures (e.g. sterilization).

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

Verification and validation of the computational model used to complete the stress/strain analysis should be carried out such that the model is credible for its context of use (see ASME V&V40[5]). The verification and validation activities completed should be commensurate with the risk associated with the use of computational model.

NOTE For guidance on verification and validation, see Reference [8].

H.2.4 Material fatigue strength determination

Material fatigue strength testing can be performed on full devices, representative surrogate test specimens, actual components (e.g. wire), or sections of components (e.g. extracted cells from the frame).

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Test specimens should be representative of the actual material in the structural component (e.g. residual stresses, plastic strains, surface condition, microstructure/defects and associated anisotropy, transformation temperature), exposed to the environments encountered in clinical fabrication (e.g. handling), and subjected to steps to which the device will be subjected prior to or during clinical use (e.g. crimping, loading, deployment, and recapture).

Stress or strain conditions (e.g. alternating and mean, principle directions), censored cycle count, and test rates/frequencies used for the fatigue strength testing will be justified by the manufacturer. Testing should be performed in an environment that is representative of the physiological environment with respect to its effect on fatigue behaviour.

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

— material processing, microstructure, composition, impurities, surface condition;

— specimen preconditioning, including loading history;

— mean and alternating stress/strain ranges used to generate the fatigue data;

— material volume at either severe stress/strain conditions or undergoing cyclic change, or both;

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

— sample size used to generate the data;

— test duration represented by the data.

H.2.5 Fatigue safety factor or probability of fatigue fracture determination

Variation in fatigue strength can result from manufacturing and material variations (e.g. surface imperfections, voids, impurities, material property variations). Variation in the stress/strain condition of the device will result from dimensional variation and variation in the in vivo boundary conditions. Deterministic or probabilistic approaches that account for these variations may be employed for fatigue resistance determinations based on risk analysis.

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

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

Fatigue to fracture testing of the device or device components may be used to validate the mode of failure, fracture location and fatigue factor of safety model.

NOTE See ASTM F3211[19].

H.3 Durability of the occluder implant

H.3.1 General

Accelerated durability testing should be conducted to demonstrate the durability of the structural and non-structural components of the cardiac occluder. Testing should be done under appropriate loading conditions. These demonstrations may be performed together in a single test or in separate tests. When appropriate, multiple demonstration tests may be used if there are multiple loading conditions.

Durability testing is typically accomplished by treating the associated results as attribute data (i.e. pass/fail) with sample sizes based upon target reliability and confidence levels. Fatigue-to-fracture

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approaches (see ASTM F3211[19]) may be used to supplement durability demonstration testing. Test rates/frequencies used for the durability testing should be justified by the manufacturer. Testing should be performed under appropriate loading conditions in a test medium at a temperature representative of the physiological environment. Testing should be performed to a minimum of 400 million cycles. A clear definition of "failure" should be established prior to testing and be consistent with the specific hazards identified by the risk analysis. If the occluder is intended for implant in multiple positions or configurations, or is available in multiple sizes, testing may be conducted in the clinically relevant challenging conditions.

H.3.2 Sample requirements

Samples shall comply with the requirements of 7.2.2.2.

The implant shall be deployed simulating the loading and deployment steps in accordance with the IFU, and appropriately placed into the test apparatus to simulate the device placement at the intended location.

The sample size should be determined based on the target reliability or confidence levels per the risk assessment.

H.3.3 Test apparatus requirements

The equipment and test procedures should be appropriate for the occluder's intended indication (e.g. adult or paediatric, anatomical position). The test fixture should be representative of the critical aspects of the target implant site, deployed size, and shape for the intended patient population. The test fixture design should be justified by the manufacturer.

When applicable, the pressure measurement system used to measure the pressure difference across the occluder should be appropriate for the cycle rate being tested and pressure waveform being measured. Minimum accuracy for the maximum differential pressure measurement should be the lesser of ±10 % or ±0,65 kPa (±5 mmHg), unless otherwise justified. The locations of the pressure transducers within the system should be appropriately justified to ensure that the differential pressure targets are achieved. The test system should be capable of accommodating the physiologic representative test fluid (e.g. buffered 0,9 % saline solution) and maintaining thermal stability of 37 °C ± 2 °C.

H.3.4 Test procedure

The deformation of the test specimen should be verified throughout the test period to be as intended at the test frequency. The test cycle rate should be established based on the device and test apparatus design and materials of construction, as these can influence the results of durability tests. Specifying test frequency without consideration to material response may result in unsatisfactory loading of the occluder. When applicable, differential pressure conditions across the occluder (see Annex O) should be applied.

The durability assessment should focus on relevant aspects of the occluder (e.g. support structure, attachments to the support structure, interactions between the occlusion component and support structure). This assessment is completed by inspection of the test occluders for damage to these relevant aspects. The failure modes considered and the acceptance criteria for the test should be determined based upon the risk assessment and defined in the protocol prior to execution of the test. Occluders undergoing cyclic durability testing should be monitored at intervals (e.g. 50 million, 100 million, 200 million, 400 million). After completion of durability testing, specimens should be subjected to detailed inspection for any evidence of structurally relevant changes (e.g. wear, fabric tear, suture hole elongation, debonding, suture fraying, microcracks or plastic slip lines in critical fatigue regions, corrosion, and fractures). A detailed description of the appearance of the occluder should be documented prior to and at the completion of testing.

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H.3.5 Test report

The durability report should include:

a) a list of the devices used to conduct the testing;

b) a description and dimensions of deployed occluder configuration;

c) a justification for the sizes and configurations tested;

d) a justification for the reference occluder (if used);

e) a justification for cycle rates used;

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

g) a description of the test fluid (e.g. biological origin or chemical components, temperature, viscosity, pH, and specific gravity under the test conditions);

h) descriptions and specifications of the test apparatus;

i) either references to or descriptions of, or both, any procedures used in order to complete the assessment;

j) a list of pertinent test conditions and their justifications (e.g. torsional, bending, axial, crush applied loads);

k) documentation of displacement or deformation of the occluder;

l) a detailed description and images of the appearance of the occluder at the prior to testing and at the defined inspection intervals;

m) an appraisal of the significance of the observed damage;

n) if the occluders met the acceptance criteria;

o) an overall conclusion regarding the accelerated durability of the occluders tested.

H.3.6 Component fatigue demonstration test

Fatigue demonstration testing of the structural components (e.g. frame, anchoring components) should be conducted under appropriate fatigue loading conditions. Component fatigue demonstration testing is typically accomplished via attribute testing methodologies with sample sizes based upon target reliability and confidence levels. Fatigue-to-fracture approaches (see ASTM F3211-17[19]) may be used to supplement fatigue demonstration testing. Test rates or frequencies used for the component fatigue testing will be justified by the manufacturer. Testing should be performed in an environment that is representative of the physiological environment with respect to its effect on fatigue behaviour. A clear definition of "failure" should be established prior to testing and be consistent with respect to the specific failure mode(s) identified by the risk analysis.

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

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

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Annex I
(normative)

Adverse event classification during clinical investigation

I.1 General

The manufacturer shall ensure that investigators evaluate and report all adverse events related to the transcatheter cardiac occluder system, 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 shall clearly identify how events are classified and reported.

I.2 Evaluation

The manufacturer shall develop pre- and post-market systems to ensure that all adverse events (i.e. serious health threat, serious adverse device effects and device deficiencies) are received, evaluated and communicated to interested parties without unjustified delay in accordance with ISO 14155 and other applicable regulations.

I.3 Data collection requirements

The manufacturer shall ensure the following information is documented on a case report form, for all observed adverse events:

a) date of onset or first observation;

b) description of the event;

c) seriousness of the event;

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

e) treatment required;

f) outcome or status of the event.

I.4 Adverse events

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

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, “medical intervention” includes a change in medication.

I.5 Adverse device effects

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

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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.

I.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. Examples of device deficiencies include but are not limited to frame fractures and device migration.

I.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 transcatheter cardiac occluder 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 timely 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 them 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 [21]).

For randomized control trials, an independent, multi-disciplinary committee of qualified experts (DSMB) shall adjudicate causality to assign the specific cause of an adverse event. Use of a DSMB is encouraged for registries. Formal adjudication of adverse events is intended to manage the ambiguity and bias in assigning causality.

Whenever feasible, autopsy 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.

I.8 Classification of adverse events

I.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 CIP be balanced against the anticipated benefits to the subjects.

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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 that occur during a clinical investigation that were not identified in the risk analysis 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 (see 3.25).

For the incidence of AEs to be compared between study cohorts or with historical data, it is important that the same definitions and methods of data collection are used. The most recent definitions of specific adverse events (e.g. see Reference [47]) shall be used for data collection on events throughout the follow-up period.

Potential adverse events identified by the risk analysis that are not included in the published guidelines shall be defined based on relevant or 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 cardiac occluder systems. Some events may potentially have more than one causality.

I.8.2 Examples of adverse events

a) Complications associated with vascular access (any of the following events with onset ≤7 d after the procedure; see Reference [47]):

   — local permanent vascular damage leading to stenosis, aneurysm, embolism or limb ischemia, peripheral ischemia/nerve injury with clinical symptoms lasting >24 h or requiring surgical repair;

   — hematoma at access site >6 cm;

   — retroperitoneal hematoma;

   — arteriovenous fistula;

   — arterial complications (either, thrombosis, stenosis or distal embolization, or all, with clinical ischemia, perforation, dissection, aneurysm, pseudoaneurysm);

   — venous complications (venous perforation, dissection, laceration);

   — symptomatic peripheral ischemia/nerve injury with clinical symptoms lasting >24 h;

   — vascular surgical or non-surgical repair at catheter access sites;

   — major bleeding (see Reference [36]);

   — pulmonary embolism;

   — venous thrombophlebitis;

   — ipsilateral deep vein thrombosis;

   — wound infection or access site related infection requiring intravenous antibiotic or extended hospitalization;

b) events associated with cardiac damage:

   — coronary artery compression;

   — cardiac perforation, including unplanned septal perforation, with or without tamponade;

   — cardiac tamponade, including late tamponade;

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- valve damage or damage to surrounding cardiac structures;
- clinically relevant atrial septal defect;
- new arrhythmia, other than very transient;
- new or worsened conduction disturbance;
- cardiac arrest;
- myocardial infarction;
- low cardiac output requiring mechanical support;
- conversion to surgery;

c) events associated with implantation procedure:

- obstruction to transvalvular flow;
- device malposition;
- device migration or embolization;
- stroke or other embolism, including coronary embolism, during the procedure or within 24 h;
- necessity for re-intervention during the initial procedure;
- obstruction or thrombosis of the coronary sinus;

d) events associated with other organ damage:

- acute kidney injury;
- respiratory failure;
- liver failure;
- septicaemia;
- haematological disorders, for example, DIC, HIT;
- pulmonary embolism;

e) potential device-related events:

- haemolysis;
- device-related infection, infective endocarditis or pericarditis;
- device embolization;
- stroke or other embolism, including coronary embolism, not clearly associated with the occluder implantation procedure;
- major bleeding;
- device erosion;
- transcatheter or surgical reintervention to repair, alter, adjust, reposition, retrieve or replace a previously implanted device (due to initial procedure);
- clinically significant device interference with surrounding structure (circumflex coronary artery, mitral valve, pulmonary artery, pulmonary vein);

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— device fracture;

— device perforation or laceration;

— device-related allergy.

I.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, and long-term outcome shall be reported.

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Annex J
(informative)

Imaging protocol

J.1 General

J.1.1 Echocardiography (e.g. TTE, TEE, ICE) is the standard imaging modality for the routine assessment of cardiac defects and occluders, both for research or regulatory studies and in clinical practice. This evaluation includes not only an assessment of the structure, position and function of the occluder, but also the effects on cardiac function.

CT, CMR and cine angiography are imaging modalities that can provide additional anatomic, physiologic and haemodynamic information. PET is a useful imaging technique in the investigation of suspected infective endocarditis and to interrogate myocardial metabolism or physiology.

Imaging prior to the implant (CT, TEE, MRI), may be useful in pre-procedural planning.

J.1.2 Imaging facilities should be equipped with systems that have been validated for the intended applications in the assessment. They should also utilize personnel that have been specifically trained to conduct the required assessments.

J.1.3 Studies should be performed according to defined protocols. Additionally, study-specific training should be conducted prior to the study to ensure that all involved personnel clearly understand protocol objectives. The protocols should include procedures for assuring the quality of the acquired data.

J.1.4 When applicable, particularly in the case of the evaluation of primary study objectives, a third party "Core Lab" should be utilized to evaluate imaging studies. The Core Lab should be selected based upon its experience in conducting these types of evaluations as well as special expertise in the selected imaging modality. Utilization of a Core Lab can improve overall study quality by eliminating centre bias, standardizing grading techniques and improving individual assessment quality. There shall be a written agreement between the sponsor and core laboratories which defines the responsibilities of each party in the clinical investigation, signed and dated by all parties involved (see ISO 14155).

J.1.5 Imaging studies should be recorded and archived for review. Data should be reviewed soon after recording a study so that deviations from the protocol can be detected early and, if necessary, a further study can be performed. A high level of interpretability is essential for unbiased data. A statement on imaging quality should include percentage of subjects imaged (if not 100 %, how they were selected), and the percentage of images which were poor, inadequate or uninterpretable.

J.1.6 Centres should minimize the number of operators performing the required exams and also the number of different machines used. Likewise, Core Labs should limit the number of observers evaluating studies.

J.1.7 For longitudinal analysis, consistent imaging methods and protocols should be used for comparison at specific time points. For example, TTE should not be mixed during any individual follow-up time-point. Likewise, protocol-specified images collected should remain consistent throughout the course of the study.

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Annex K
(informative)

Clinical investigation endpoints for transcatheter cardiac occluders: Suggestions for endpoints and their timing

K.1 General

Due to the vast variety of occluders, indications and patient populations, the endpoints listed herein are only minimum requirements and not an exhaustive list. Endpoints should reflect patient safety and benefit such as living longer, feeling better or functioning better. Validated surrogate endpoints for clinical benefit have a place in the investigation design to increase the information gained by an investigation and to possibly decrease the sample size needed and the length of time required for the investigations. The ability to compare clinical investigations and to create useful observational registries requires the use of standardized definitions of endpoint components.

Endpoints reported at specific times should be prespecified and justified. Some possible endpoints, such as mortality, can be considered both a safety and effectiveness endpoint. The endpoints are divided into safety and effectiveness endpoints.

K.2 Single endpoints

K.2.1 General

The clinical investigation should follow the most recent guidelines for safety and effectiveness endpoints.

K.2.2 Safety

These endpoints for safety should be considered, at minimum:

- mortality:
  - all-cause mortality,
  - cardiovascular mortality,
  - non-cardiovascular mortality, and
  - procedural mortality (30 d (unless otherwise justified) from procedure or discharge from the hospital, whichever is longer);
- neurological events:
  - stroke,
    - stroke severity,
      - non-disabling stroke,
      - disabling stroke,
    - stroke classification,
      - ischaemic,

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        - haemorrhagic, and
    - transient ischaemic events;
- systemic thromboembolism;
- acute kidney injury;
- myocardial infarction;
- device events:
    - embolization,
    - malposition,
    - loss of structural integrity, and
    - thrombosis;
- infective endocarditis;
- access site events:
    - major access site events, and
    - minor access site events;
- bleeding:
    - major bleeding, and
    - minor bleeding;
- haemolysis;
- severe conduction disturbances, including new permanent pacemaker implantation.

Additional safety endpoints should be considered based upon the patient population, the investigational design and the device.

The following performance or effectiveness endpoints should be considered based upon the patient population, the investigational design and the device. Other performance or effectiveness endpoints may be selected as applicable.

K.2.3 Performance and effectiveness

These endpoints for performance and effectiveness should be considered, at minimum, to include:

- residual leak;
- patient functional status (e.g. New York Heart Association class);
- patient reported outcomes (e.g. Kansas City Cardiomyopathy Questionnaire, EuroQOL, Medical Outcomes Study Short Form – 36, Short Form - 12), when applicable;
- thromboembolic events.

Continued evidence of device success should be present at the time of primary effectiveness endpoint assessment to support the determination that any observed clinical benefit was due to the implanted device.

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K.3 Composite endpoints

The choice of the components of the composite endpoints depends on the device used, the patient population, and the design of the investigation. Abbreviations such as MACE (Major Adverse Cardiac Events) should be specified or defined because of the lack of universal agreement on the components of this safety endpoint.

Most of the time composite endpoints are not hierarchically ranked as to their clinical importance or their frequency of occurrence. Therefore, a relatively less clinically important endpoint can disproportionally influence the results of an investigation. For example, a common composite endpoint in invasive device investigations is death, stroke, and bleeding. It is possible that an investigation with this composite endpoint can meet its endpoint because of decreased bleeding while having greatly increased death and stroke rates. The use of a single composite clinical safety and effectiveness endpoint, especially when the individual components of safety and efficacy move in opposite directions, is not recommended.

K.4 Timing of endpoints

The selection of the time at which the primary endpoints in a study are evaluated is critical for evaluating both safety and effectiveness. The time depends on the patient population studied as well as the type of device and the intended use of the device. A patient population with a limited life expectancy may have a shorter time for the primary endpoint that a younger, healthier population. A device with common technological characteristics can have a shorter endpoint time than a life-sustaining device with untested technology. A study that has separate safety and effectiveness endpoints may have different times for evaluation of these endpoints. Procedural endpoints are commonly assessed at 30 d or when the patient is discharged from the hospital, whichever is longer.

Patients should be consented for the full duration of the study follow-up. In addition, studies should collect all events during the full duration of the study follow-up, not only first events, and should present an analysis of the intervention using both linearized rates and Kaplan-Meier analysis.

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